PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 333/38, A61K 31/415, 31/495, 31/435, C07D 409/12, 409/14, 417/14, 333/70, 409/06, 473/06, 473/34
A1

(11) International Publication Number: WO 99/32477
(43) International Publication Date: 1 July 1999 (01.07.99)

(21) International Application Number: PCT/EP98/07650
(22) International Filing Date: 27 November 1998 (27.11.98)
(30) Priority Data:
08/994,284 19 December 1997 (19.12.97) US
09/187,459 5 November 1998 (05.11.98) US

(71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE).

(72) Inventors: ARNAIZ, Damian, O.; 103 Bedford, Hercules, CA 94547 (US). CHOU, Yuo-Ling; 1068 Miller Drive, Lafayette, CA 94549 (US). KARANJAWALA, Rushad, E.; 172 Bonaire Avenue, Hercules, CA 94547 (US). KOCHANNY, Monica, J.; 193 Irwin Street, San Rafael, CA 94901 (US). LEE, Wheesong; 933 Hough Avenue #10, Lafayette, CA 94549 (US). LIANG, Amy, Mei; 5572 Cerro Norte, Richmond, CA 94803 (US). MORRISSEY, Michael, M.; 129 Alta Vista, Danville, CA 94506 (US). PHILLIPS, Gary, B.; 3043 Shetland Drive, Pleasant Hill, CA 94523 (US). SACCHI, Karna, Lyn; 202 Clipper Street #1, San Francisco, CA 94114 (US). SAKATA, Stephen, T.; 1411 Palo Verde Road, Irvine, CA 92612 (US). SHAW, Kenneth, J.; 16 Oakmont Court, San Rafael, CA 94901 (US). SNIDER, R., Michael; 1031 Lorraine Drive, Napa, CA 94558 (US). WU, Shung, C.; 7121 Foxtail Court, Lawrenceville, NJ 08648 (US). YE, Bin; Apartment 3022, 3400 Richmond Parkway, Richmond, CA 94806 (US). ZHAO, Zuchun; 5368 Cerro Sur, El Sobrante, CA 94803 (US). GRIEDEL, Brian, D.; 526 Liberty Street, El Cerrito, CA 94530 (US).

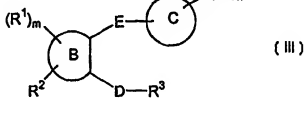
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: *ORTHO*-ANTHRANILAMIDE DERIVATIVES AS ANTI-COAGULANTS

(57) Abstract

This invention is directed to compounds of formula (III) wherein B, C, D, E, R^1, R^2 and R^3 are disclosed herein. These compounds are disclosed as being useful as anti-coagulants.



(III)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ORTHO-ANTHRANILAMIDE DERIVATIVES AS ANTI-COAGULANTS

Field of the Invention

The present invention is directed to *ortho*-anthranilamide derivatives and their pharmaceutically acceptable salts, which inhibit the enzyme, factor Xa, thereby being useful as anti-coagulants. It also relates to pharmaceutical compositions containing the derivatives or their pharmaceutically acceptable salts, and methods of their use.

BACKGROUND OF THE INVENTION

Factor Xa is a member of the trypsin-like serine protease class of enzymes. A one-to-one binding of factors Xa and Va with calcium ions and phospholipid forms the prothrombinase complex which converts prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin which polymerizes to form insoluble fibrin.

In the coagulation cascade, the prothrombinase complex is the convergent point of the intrinsic (surface activated) and extrinsic (vessel injury-tissue factor) pathways (*Biochemistry* (1991), Vol. 30, p. 10363; and *Cell* (1988), Vol. 53, pp. 505-518). The model of the coagulation cascade has been refined further with the discovery of the mode of action of tissue factor pathway inhibitor (TFPI) (*Seminars in Hematology* (1992), Vol. 29, pp. 159-161). TFPI is a circulating multi-domain serine protease inhibitor with three Kunitz-type domains which competes with factor Va for free factor Xa. Once formed, the binary complex of factor Xa and TFPI becomes a potent inhibitor of the factor VIIa and tissue factor complex.

Factor Xa can be activated by two distinct complexes, by tissue factor-VIIa complex on the "Xa burst" pathway and by the factor IXa-VIIIa complex (TENase) of the "sustained Xa" pathway in the coagulation cascade. After vessel injury, the "Xa burst" pathway is activated *via* tissue factor (TF). Up regulation of the coagulation cascade occurs *via* increased factor Xa production *via* the "sustained Xa" pathway. Down regulation of the coagulation cascade occurs with the formation of the factor Xa-TFPI complex, which not only removes factor Xa but also inhibits further factor formation *via* the "Xa burst" pathway. Therefore, the coagulation cascade is naturally regulated by factor Xa.

The primary advantage of inhibiting factor Xa over thrombin in order to prevent coagulation is the focal role of factor Xa versus the multiple functions of thrombin. Thrombin not

only catalyzes the conversion of fibrinogen to fibrin, factor VIII to VIIIA, factor V to Va, and factor XI to XIa, but also activates platelets, is a monocyte chemotactic factor, and mitogen for lymphocytes and smooth muscle cells. Thrombin activates protein C, the *in vivo* anti-coagulant inactivator of factors Va and VIIIa, when bound to thrombomodulin. In circulation, thrombin is rapidly inactivated by antithrombin III (ATIII) and heparin cofactor II (HCII) in a reaction which is catalyzed by heparin or other proteoglycan-associated glycosaminoglycans, whereas thrombin in tissues is inactivated by the protease, nexin. Thrombin carries out its multiple cellular activation functions through a unique "tethered ligand" thrombin receptor (*Cell* (1991), Vol. 64, p. 1057), which requires the same anionic binding site and active site used in fibrinogen binding and cleavage and by thrombomodulin binding and protein C activation. Thus, a diverse group of *in vivo* molecular targets compete to bind thrombin and the subsequent proteolytic events will have very different physiological consequences depending upon which cell type and which receptor, modulator, substrate or inhibitor binds thrombin.

Published data with the proteins antistasin and tick anti-coagulant peptide (TAP) demonstrate that factor Xa inhibitors are efficacious anti-coagulants (*Thrombosis and Haemostasis* (1992), Vol. 67, pp. 371-376; and *Science* (1990), Vol. 248, pp. 593-596).

The active site of factor Xa can be blocked by either a mechanism-based or a tight binding inhibitor (a tight binding inhibitor differs from a mechanism-based inhibitor by the lack of a covalent link between the enzyme and the inhibitor). Two types of mechanism-based inhibitors are known, reversible and irreversible, which are distinguished by ease of hydrolysis of the enzyme-inhibitor link (*Thrombosis Res* (1992), Vol. 67, pp. 221-231; and *Trends Pharmacol. Sci.* (1987), Vol. 8, pp. 303-307). A series of guanidino compounds are examples of tight-binding inhibitors (*Thrombosis Res.* (1980), Vol. 19, pp. 339-349). Arylsulfonyl-arginine-piperidine-carboxylic acid derivatives have also been shown to be tight-binding inhibitors of thrombin (*Biochem.* (1984), Vol. 23, pp. 85-90), as well as a series of arylamidine-containing compounds, including 3-amidinophenylaryl derivatives (*Thrombosis Res.* (1983), Vol. 29, pp. 635-642) and bis(amidino)benzyl cycloketones (*Thrombosis Res.* (1980), Vol. 17, pp. 545-548). However, these compounds demonstrate poor selectivity for factor Xa.

Related Disclosures

European Published Patent Application 0 540 051 (Nagahara *et al.*) describes aromatic amidine derivatives. These derivatives are stated to be capable of showing a strong anticoagulant effect through reversible inhibition of factor Xa.

The synthesis of α,α'-bis(amidinobenzylidene)cycloalkanones and

α,α'-bis(amidino-benzyl)cycloalkanones is described in *Pharmazie* (1977), Vol. 32, No. 3, pp. 141-145. These compounds are disclosed as being serine protease inhibitors.

U.S. Patent No. 5,612,363 (Mohan *et al.*) describes *N,N*-di(aryl) cyclic urea derivatives. These compounds are stated to be factor Xa inhibitors, thereby being useful as anticoagulants.

U.S. Patent No. 5,633,381 (Dallas *et al.*) describes (Z,Z), (Z,E) and (E,Z) isomers of substituted *bis*(phenylmethylene)cycloketones. These compounds are disclosed as being factor Xa inhibitors, thereby being useful as anticoagulants.

U.S. Patent No. 5,691,364 (Buckman *et al.*) describes benzamidine derivatives. These compounds are stated to be factor Xa inhibitors, thereby being useful as anticoagulants.

PCT Published Patent Application WO/97/21437 (Arnaiz *et al.*) describes naphthyl-substituted benzimidazole derivatives. These compounds are disclosed as being factor Xa inhibitors, thereby being useful as anticoagulants.

PCT Published Patent Application WO/97/29067 (Kochanny *et al.*) describes benzamidine derivatives that are substituted by amino acid and hydroxy acid derivatives. These compounds are stated to be factor Xa inhibitors, thereby being useful as anticoagulants.

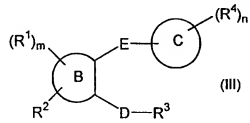
PCT Published Patent Applications WO/96/10022 (Faull *et al.*), WO97/29104 (Faull *et al.*), and WO/97/28129 describe aminoheterocyclic compounds which are disclosed as being factor Xa inhibitors, thereby being useful as antithrombotics and anticoagulants.

The above references, published patent applications and U.S. patents are herein incorporated in full by reference.

SUMMARY OF THE INVENTION

This invention is directed to compounds or their pharmaceutically acceptable salts which inhibit human factor Xa and are therefore useful as pharmacological agents for the treatment of disease-states characterized by thrombotic activity, *i.e.*, as anti-coagulants.

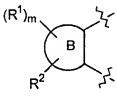
Accordingly, in one aspect, this invention provides compounds of formula (III):



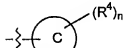
wherein

m is 1 to 3;

n is 1 to 5;



is an aryl or a heterocyclic ring substituted by R^2 and one or more R^1 groups;



is an aryl or a heterocyclic ring substituted by one or more R^4 groups;

D and E are independently a linker selected from the group consisting of $-N(R^5)-C(X)-$; $-R^8-N(R^5)-C(X)-$; $-N(R^5)-C(X)-R^8-$; $-R^8-N(R^5)-C(X)-R^8-$; $-N(R^5)-S(O)_p-$; $-R^8-N(R^5)-S(O)_p-$; $-N(R^5)-S(O)_p-R^8-$; and $-R^8-N(R^5)-S(O)_p-R^8-$ (where p is 0 to 2; X is oxygen, sulfur or H_2) where D and E can be attached to the B ring having the R^1 and R^2 substituents by either terminus of the selected linker;

each R^1 is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^5)R^6$, $-O-C(O)R^5$, $-N(R^5)-CH(R^{12})-C(O)OR^5$, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$) or heterocyclylalkyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$);

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-R^8-N(R^{10})R^{11}$, $-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-S(O)_p-R^9$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-O-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-C(R^7)H-N(R^5)R^6$, $-C(R^7)H-R^8-N(R^5)R^6$, $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$, $-O-R^8-N(R^{10})R^{11}$, $-O-R^8-O-C(O)R^5$, $-O-R^8-CH(OH)-CH_2-OR^5$, $-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-(R^8-O)_t-R^{19}$ (where t is 1 to 6), $-O-R^8-C(O)R^5$, $-O-R^8-C(O)R^{19}$, $-O-R^8-C(O)OR^5$, $-N(R^5)-R^8-N(R^{10})R^{11}$, $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2), $-S(O)_p-R^8-C(O)OR^5$ (where p is 0 to 2), or $-N(R^5)-CH(R^{12})-C(O)OR^5$;

R^3 is aryl or heterocyclyl both substituted by one or more R^{14} substituents independently selected from the group consisting of hydrogen, alkyl, halo, formyl, acetyl, cyano, $-R^8-CN$, $-N(R^{10})R^{11}$, $-R^8-N(R^{10})R^{11}$, $-R^8-N^{\oplus}(R^8)(R^{16})_2$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-OR^5$, $-R^8-OR^5$, $-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-(R^8-O)_t-R^5$

(where t is 1 to 6), $-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-R^8-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, $-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-O-N(R^5)R^6$, heterocyclyl (wherein the heterocyclyl radical is not attached to the rest of the molecule through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), and heterocyclylalkyl (wherein the heterocyclyl radical is not attached to the alkyl radical through a nitrogen ring and is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^8$, $-C(O)N(R^5)R^6$, or $-R^8-N(R^5)R^6$;

each R^5 and R^6 is independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{10} and R^{11} is independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^8$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{18})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^8$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is

0 to 2), -$(R^8\text{-}O)_t\text{-}R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6, and -C(O)N(R^5)R^6);

R^{12} is a side chain of an α-amino acid;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R^8-O-C(O)-R^5, -R^8-OR^5, -N(R^5)R^6, -R^8-N(R^5)R^6, -R^8-C(O)OR^5, heterocydyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -R^8-OR^5, -C(O)OR^5, -N(R^5)R^6, and -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -R^8-OR^5, -C(O)OR^5, -N(R^5)R^6, and -C(O)N(R^5)R^6);

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, OR^5, -C(O)OR^5, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R^{16} is independently alkyl, aryl, aralkyl, -R^8-OR^5, -R^8-N(R^5)R^6, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR^5), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 or -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 and -C(O)N(R^5)R^6); or

both R^{16}'s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR^5, -R^8-OR^5, -C(O)OR^5, -R^8-C(O)OR^5, -N(R^5)R^8, -R^8-N(R^5)R^6, -C(O)R^5, -C(O)-$(R^8\text{-}O)_t\text{-}R^5$ (where t is 1 to 6), and -$(R^8\text{-}O)_t\text{-}R^5$ (where t is 1 to 6);

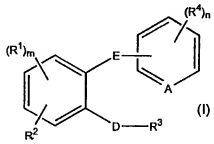
each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR^5, -R^8-OR^5, -C(O)OR^5, -R^8-C(O)OR^5, -C(O)-N(R^5)R^6, or -R^8-C(O)-N(R^5)R^6;

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR^5, or -NO_2; and

each R^{19} is cycloalkyl, haloalkyl, -R^8-OR^5, -R^8-N(R^5)R^6, -R^8-C(O)OR^5, -R^8-C(O)N(R^5)R^6, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 or -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 and -C(O)N(R^5)R^6);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides compounds of formula (I):



(I)

A is =CH- or =N-;

m is 1 to 3;

n is 1 to 4;

D is -N(R^5)-C(Z)- or -N(R^5)-S(O)$_p$- (where p is 0 to 2; Z is oxygen, sulfur or H_2; and the nitrogen atom is directly bonded to the phenyl ring having the R^1 and R^2 substituents);

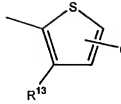
E is -C(Z)-N(R^5)- or -S(O)$_p$-N(R^5)- (where p is 0 to 2; Z is oxygen, sulfur or H_2; and the nitrogen atom can be bonded to the phenyl ring having the R^1 and the R^2 substituents or to the aromatic ring having the R^4 substituent);

each R^1 is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR^5, -S(O)$_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -C(O)N(R^5)R^6, -N(R^5)R^6, -O-C(O)R^5, or -N(R^5)-CH(R^{12})-C(O)OR^5;

or two adjacent R^1's together with the carbons to which they are attached form a heterocyclic ring fused to the phenyl ring wherein the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl and aralkyl;

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR^5, -S(O)$_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -OC(O)-R^5, -C(O)N(R^5)R^6, -N(R^{10})R^{11}, -C(R^7)H-N(R^{10})R^{11}, -C(R^7)H-R^8-N(R^{10})R^{11}, -C(R^7)H-OR^5, -C(R^7)H-R^8-OR^5, -C(R^7)H-S(O)$_p$-R^9 (where p is 0 to 2), -C(R^7)H-R^8-S(O)$_p$-R^9 (where p is 0 to 2), -O-R^8-S(O)$_p$-R^9 (where p is 0 to 2), -C(R^7)H-N(R^5)R^6, -C(R^7)H-R^8-N(R^5)R^6, -O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}, -O-R^8-N(R^{10})R^{11}, -O-R^8-O-C(O)R^5, -O-R^8-CH(OH)-CH_2-OR^5, -O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -O-(R^8-O)$_t$-R^{19} (where t is 1 to 6), -O-R^8-C(O)R^5, -O-R^8-C(O)R^{19}, -O-R^8-C(O)OR^5, -N(R^5)-R^8-N(R^{10})R^{11}, -S(O)$_p$-R^8-N(R^5)R^6 (where p is 0 to 2), -S(O)$_p$-R^8-C(O)OR^5 (where p is 0 to 2), or -N(R^5)-CH(R^{12})-C(O)OR^5;

R^3 is a radical of formula (i):



(i)

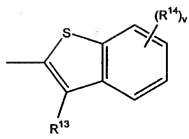
where:

r is 1 or 2;

R^{13} is hydrogen, alkyl, halo, haloalkyl, $-N(R^5)R^6$, $-C(R^7)H-N(R^5)R^6$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2) or heterocyclylalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, cyano, $-R^8-CN$, $-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-R^8-N(R^{10})R^{11}$, $-C(R^7)H-N^{\oplus}(R^9)(R^{16})_2$, $-C(R^7)H-R^8-N^{\oplus}(R^9)(R^{16})_2$, $-C(O)OR^5$, $-C(R^7)H-C(O)OR^5$, $-C(R^7)H-R^8-C(O)OR^5$, $-OR^5$, $-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-C(R^7)H-C(O)N(R^5)R^6$, $-C(R^7)H-R^8-C(O)N(R^5)R^6$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, $-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-O-N(R^5)R^6$, heterocyclyl (wherein the heterocyclyl radical is not attached to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (wherein the heterocyclyl radical is not attached to the alkyl radical through a nitrogen atom and is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^3 is a radical of the formula (ii):



(ii)

where v is 1 to 4;

R^{13} is as defined above for formula (i); and

R^{14} is as defined above for formula (i);

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, or $-R^8-N(R^5)R^6$;

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{18})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or

more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

R^{12} is a side chain of an α-amino acid;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$); or

both R^{16}'s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6);

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$;

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-C(O)OR^5$, or $-NO_2$; and

each R^{19} is cycloalkyl, haloalkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-R^8-C(O)N(R^5)R^6$, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof;

provided that when A is =CH-, m is 1, n is 1, D is -N(H)-C(O)- (where the nitrogen atom is directly bonded to the phenyl ring having the R^1 and R^2 substituents), E is -C(O)-N(H)- (where the nitrogen atom is directly bonded to the phenyl ring having the R^4 substitutent), R^1 is hydrogen and R^2 is in the 5-position and is methyl, R^4 is in the 4-position and is fluoro, R^3 can not be a radical of formula (ii) where v is 1, R^{14} is hydrogen, and R^{13} is chloro.

In another aspect, this invention provides compositions useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound of the invention as described above, without the proviso, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, this invention provides a method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above, without the proviso.

In another aspect, this invention provides a method of treating a human having a disease-state alleviated by the inhibition of factor Xa, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above, without the proviso.

In another aspect, this invention provides a method of inhibiting human factor Xa *in vitro* by the administration of a compound of the invention, without the proviso.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above, *e.g.*, methoxy, ethoxy, propoxy, and the like.

"Alkoxyalkyl" refers to a radical of the formula $-R_a-OR_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, 2-methoxyethyl, methoxymethyl, 3-ethoxypropyl, and the like.

"Alkylene chain" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to six carbon

atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene and the like.

"Alkylidene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to six carbon atoms, wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule, *e.g.,* ethylidene, propylidene, *n*-butylidene, and the like.

"Alkylidyne chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to six carbon atoms, wherein the unsaturation is present only as triple bonds and wherein a triple bond can exist between the first carbon of the chain and the carbon atom of the rest of the molecule to which it is attached, *e.g.*, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like.

"Amino" refers to the $-NH_2$ radical.

"Aminocarbonyl" refers to the $-C(O)NH_2$ radical.

"Aryl" refers to a phenyl or naphthyl radical. Unless otherwise indicated, the term "aryl" refers to phenyl or naphthyl radicals which are optionally substituted by alkyl, halo, $-OR^5$ (where R^5 is hydrogen, alkyl, aryl or aralkyl).

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical, as defined above, substituted by R_b, an aryl radical, as defined above, *e.g.*, benzyl.

"α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, ornithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, *ortho*-tyrosine, *meta*-tyrosine, *para*-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

"Cycloalkyl" refers to a 3- to 7-membered monocyclic cyclic radical which is saturated, and which consists solely of carbon and hydrogen atoms, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"DMF" refers to *N,N*-dimethylformamide.

"DMSO" refers to dimethylsulfoxide.

"Dialkylamino" refers to a radical of the formula $-N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylamino, diethylamino, (*iso*-propyl)(ethyl)amino, and the like.

"Dialkylaminocarbonyl" refers to a radical of the formula $-C(O)N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, (dimethylamino)carbonyl, (diethylamino)carbonyl, ((*iso*-propyl)(ethyl)amino)carbonyl, and the like.

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Heterocyclic ring" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems, and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl and oxadiazolyl. For those compounds where two adjacent R^1's together with the carbons to which they are attached form a heterocyclic ring fused to the phenyl ring, the most preferred heterocyclic ring is the dioxolane ring (with the phenyl ring forms a benzodioxole ring).

"Heterocyclyl" refers to a heterocyclic ring radical as defined above, except that the heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

"Heterocyclylalkyl" refers to a radical of the formula $-R_a-R_c$ where R_a is an alkyl radical as defined above and R_c is a heterocyclyl ring radical as defined above, for example, (4-methylpiperazin-1-yl)methyl, (morpholin-4-yl)methyl, 2-(oxazolin-2-yl)ethyl, and the like.

"*N*-heterocyclic ring" refers to those heterocyclic ring radicals defined above which contain at least one nitrogen. The *N*-heterocyclic ring radical is attached to the main structure through a nitrogen atom in the ring. Examples include, but are not limited to, 4-methylpiperazin-1-yl, pyrrolidin-1-yl, morpholin-4-yl, oxazolin-2-yl, and the like. The *N*-heterocyclic ring may contain up to three additional hetero atoms. Examples include tetrazolyl, triazolyl, thiomorpholinyl, oxazinyl, and the like.

"HPLC" refers to high pressure liquid chromatography.

"Monoalkylamino" refers to a radical of the formula $-N(H)R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylamino, ethylamino, (*t*-butyl)amino, and the like.

"Monoalkylaminocarbonyl" refers to a radical of the formula $-C(O)N(H)R_a$ where R_a is an alkyl radical as defined above, *e.g.*, (methylamino)carbonyl, (ethylamino)carbonyl, ((*t*-butyl)amino)carbonyl, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of

primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a human in need thereof, is sufficient to effect treatment, as defined below, for disease-states characterized by thrombotic activity. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease-state and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"THF" refers to tetrahydrofuran.

"Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by thrombotic activity, and includes:

(i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it;

(ii) inhibiting the disease-state, *i.e.*, arresting its development; or

(iii) relieving the disease-state, *i.e.*, causing regression of the disease-state.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

For purposes of this invention, in the substituent "-R^8-OR^{5n}", the "-OR^{5n}" group may be attached to any carbon in the alkylene, alkylidene or alkylidyne chain.

Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclic ring systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, *i.e.*, amino, imino, hydroxy or oxo, respectively.

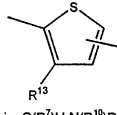
For purposes of this invention, unless otherwise indicated, the linker moieties between the B ring and the C ring ("E") and between the B ring and the R^3 moiety ("D") may be independently attached to the B ring on either end of the linker.

For purposes of this invention, the quaternary salts represented by "-$N^{\oplus}(R^9)(R^{16})_2$" include

aromatic rings wherein both R^{16}'s together with the nitrogen to which they are attached form an aromatic ring and it is understood that R^9 is not present.

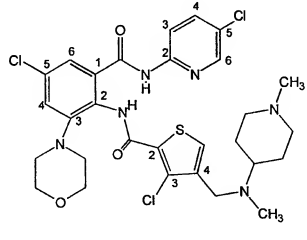
The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention. Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art.

The nomenclature used herein is a modified form of the I.U.P.A.C. system wherein the compounds of the invention are named as derivatives of benzamide. For example, a compound of the invention selected from formula (I) where A is -N-; m is 1; n is 1; E is -C(O)-N(H)- where the nitrogen atom is bonded to pyridine ring; D is -N(H)-C(O)- where the nitrogen atom is bonded to the phenyl ring; R^1 is in the 5-position and is chloro; R^2 is in the 3-position and is $-N(R^{10})R^{11}$ where R^{10} and R^{11} together with nitrogen to which they are attached form a morpholin-4-yl ring; R^4 is in the 5-position and is chloro; and R^3 is selected from formula (i):



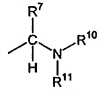
(i)

where R^{13} is chloro,r is 1 and R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^7 is hydrogen, R^{10} is methyl and R^{11} is 1-methylpiperidin-4-yl; *i.e.*, a compound of the following formula (with position numbers indicated):



is named herein as *N*-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide.

For purposes of this specification, parenthesis are used to denote substituents of a main atom. For example, $-C(R^7)H-N(R^{10})R^{11}$ refers to the radical:



Carbonyl and thiocarbonyl groups are indicated as -C(O)- and -C(S)-, respectively, and optionally substituted imino radicals are indicated as $=N(R^{17})$.

Substituents having repeating sections are indicated by brackets (or parenthesis) and the repeating integer. For example, the substituent $-C(R^7)H-R^8-(R^8-O)_t-R^5$ where t is 3 refers to the the substituent $-C(R^7)H-R^8-R^8-O-R^8-O-R^8-O-R^5$.

Utility and Administration

A. Utility

The compounds of the invention are inhibitors of the serine protease, factor Xa, and are therefore useful in disease-states characterized by thrombotic activity based on factor Xa's role in the coagulation cascade (see Background of the Invention above). Primarily, the compounds of the invention are useful as anti-coagulants. A primary indication for the compounds is prophylaxis for long term risk following myocardial infarction. Additional indications are prophylaxis of deep vein thrombosis (DVT) following orthopedic surgery or prophylaxis of selected patients following a transient ischemic attack. The compounds of the invention may also be useful for indications in which coumarin is currently used, such as for DVT or other types of surgical intervention such as coronary artery bypass graft and percutaneous transluminal coronary angioplasty. The compounds are also useful for the treatment of thrombotic complications associated with acute promyelocytic leukemia, diabetes, multiple myelomas, disseminated intravascular coagulation associated with septic shock, purpura fulminanas associated infection, adult respiratory distress syndrome, unstable angina, and thrombotic complications associated with aortic valve or vascular prosthesis. The compounds are also useful for prophylaxis for thrombotic diseases, in particular in patients who have a high risk of developing such disease.

In addition, the compounds of the invention are useful as *in vitro* diagnostic reagents for selectively inhibiting factor Xa without inhibiting other components of the coagulation cascade.

B. Testing

The primary bioassays used to demonstrate the inhibitory effect of the compounds of the invention on factor Xa are simple chromogenic assays involving only serine protease, the compound of the invention to be tested, substrate and buffer (see, *e.g.*, *Thrombosis Res.* (1979), Vol. 16, pp. 245-254). For example, four tissue human serine proteases can be used in the primary bioassay, free factor Xa, prothrombinase, thrombin (IIa) and tissue plasminogen activator (tPA). The assay for tPA has been successfully used before to demonstrate undesired side effects in the inhibition of the fibrinolytic process (see, *e.g.*, *J. Med. Chem.* (1993), Vol. 36, pp. 314-319).

Another bioassay useful in demonstrating the utility of the compounds of the invention in inhibiting factor Xa demonstrates the potency of the compounds against free factor Xa in citrated plasma. For example, the anticoagulant efficacy of the compounds of the invention will be tested using either the prothrombin time (PT), or activated partial thromboplastin time (aPTT) while selectivity of the compounds is checked with the thrombin clotting time (TCT) assay. Correlation of the K_i in the primary enzyme assay with the K_i for free factor Xa in citrated plasma will screen against compounds which interact with or are inactivated by other plasma components. Correlation of the K_i with the extension of the PT is a necessary *in vitro* demonstration that potency in the free factor Xa inhibition assay translates into potency in a clinical coagulation assay. In addition, extension of the PT in citrated plasma can be used to measure duration of action in subsequent pharmacodynamic studies.

For further information on assays to demonstrate the activity of the compounds of the invention, see R. Lottenberg *et al.*, *Methods in Enzymology* (1981), Vol. 80, pp. 341-361, and H. Ohno *et al.*, *Thrombosis Research* (1980), Vol. 19, pp. 579-588.

C. General Administration

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out *via* any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a

compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, *etc.*

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease-state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharin, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like.

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, *e.g.*, polyoxyethylene glycols and polyethylene glycols (PEG), *e.g.*, PEG 1000 (96%) and PEG 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, *etc.*, a compound(s) of the invention (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, *etc.*

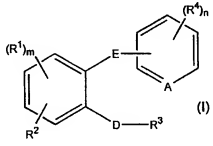
Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state alleviated by the inhibition of factor Xa in accordance with the teachings of this invention.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disease-states; and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.14 mg to about 14.3 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.7 mg to about 10 mg/kg of body weight per day; and most preferably, from about 1.4 mg to about 7.2 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 10 mg to about 1.0 gram per day of a compound of the invention, or a pharmaceutically acceptable salt thereof, preferably from about 50 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day.

Preferred Embodiments

Of the compounds disclosed in the Summary of the Invention, certain compounds are preferred.

The most preferred compounds of the invention are those compounds selected from formula (III) having the formula (I):



(I)

A is =CH- or =N-;

m is 1 to 3;

n is 1 to 4;

D is -N(R^5)-C(Z)- or -N(R^5)-S(O)$_p$- (where p is 0 to 2; Z is oxygen, sulfur or H_2; and the nitrogen atom is directly bonded to the phenyl ring having the R^1 and R^2 substituents);

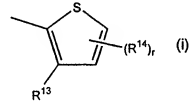
E is -C(Z)-N(R^5)- or -S(O)$_p$-N(R^5)- (where p is 0 to 2; Z is oxygen, sulfur or H_2; and the nitrogen atom can be bonded to the phenyl ring having the R^1 and the R^2 substituents or to the aromatic ring having the R^4 substituent);

each R^1 is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR^5, -S(O)$_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -C(O)N(R^5)R^8, -N(R^5)R^6, -O-C(O)R^5, or -N(R^5)-CH(R^{12})-C(O)OR^5;

or two adjacent R^1's together with the carbons to which they are attached form a heterocyclic ring fused to the phenyl ring wherein the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl and aralkyl;

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR^5, -S(O)$_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -OC(O)-R^5, -C(O)N(R^5)R^6, -N(R^{10})R^{11}, -C(R^7)H-N(R^{10})R^{11}, -C(R^7)H-R^8-N(R^{10})R^{11}, -C(R^7)H-OR^5, -C(R^7)H-R^8-OR^5, -C(R^7)H-S(O)$_p$-R^9 (where p is 0 to 2), -C(R^7)H-R^8-S(O)$_p$-R^9 (where p is 0 to 2), -O-R^8-S(O)$_p$-R^9 (where p is 0 to 2), -C(R^7)H-N(R^5)R^6, -C(R^7)H-R^8-N(R^5)R^6, -O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}, -O-R^8-N(R^{10})R^{11}, -O-R^8-O-C(O)R^5, -O-R^8-CH(OH)-CH_2-OR^5, -O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -O-(R^8-O)$_t$-R^{19} (where t is 1 to 6), -O-R^8-C(O)R^5, -O-R^8-C(O)R^{19}, -O-R^8-C(O)OR^5, -N(R^5)-R^8-N(R^{10})R^{11}, -S(O)$_p$-R^8-N(R^5)R^6 (where p is 0 to 2), -S(O)$_p$-R^8-C(O)OR^5 (where p is 0 to 2), or -N(R^5)-CH(R^{12})-C(O)OR^5;

R^3 is a radical of formula (i):



(i)

where:

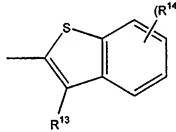
r is 1 or 2;

R^{13} is hydrogen, alkyl, halo, haloalkyl, -N(R^5)R^6, -C(R^7)H-N(R^5)R^6, -OR^5, -R^8-OR^5, -S(O)$_p$-R^8-N(R^5)R^6 (where p is 0 to 2) or heterocyclylalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, cyano, -R^8-CN, -N(R^{10})R^{11}, -C(R^7)H-N(R^{10})R^{11}, -C(R^7)H-R^8-N(R^{10})R^{11}, -C(R^7)H-$N^{\oplus}$(R^8)(R^{16})$_2$,

$-C(R^7)H-R^8-N^{\oplus}(R^9)(R^{15})_2$, $-C(O)OR^5$, $-C(R^7)H-C(O)OR^5$, $-C(R^7)H-R^8-C(O)OR^5$, $-OR^5$, $-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-C(R^7)H-C(O)N(R^5)R^6$, $-C(R^7)H-R^8-C(O)N(R^5)R^8$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-R^8-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, $-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-C(NR^{17})-N(R^5)R^8$, $-C(R^7)H-O-N(R^5)R^8$, heterocyclyl (wherein the heterocyclyl radical is not attached to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (wherein the heterocyclyl radical is not attached to the alkyl radical through a nitrogen atom and is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^3 is a radical of the formula (ii):



(ii)

where v is 1 to 4;

R^{13} is as defined above for formula (i); and

R^{14} is as defined above for formula (i);

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, or $-R^8-N(R^5)R^6$;

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$,

$-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^8$, $-C(N(R^5)R^6)=C(R^{16})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^8$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^8$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

R^{12} is a side chain of an α-amino acid;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$,

-C(O)OR^5, -N(R^5)R^6 or -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 and -C(O)N(R^5)R^6); or

both R^{16}'s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR^5, -C(O)OR^5, -R^8-C(O)OR^5, -N(R^5)R^6, -R^8-N(R^5)R^6, -C(O)R^5, -C(O)-(R^8-O)$_t$-R^5 (where t is 1 to 6), and -(R^8-O)$_t$-R^5 (where t is 1 to 6);

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR^5, -R^8-OR^5, -C(O)OR^5, -R^8-C(O)OR^5, -C(O)-N(R^5)R^6, or -R^8-C(O)-N(R^5)R^6;

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR^5, or -NO$_2$; and

each R^{19} is cycloalkyl, haloalkyl, -R^8-OR^5, -R^8-N(R^5)R^6, -R^8-C(O)OR^5, -R^8-C(O)N(R^5)R^6, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 or -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -C(O)OR^5, -N(R^5)R^6 and -C(O)N(R^5)R^6).

Of these compounds, a preferred group of compounds are those compounds wherein:

A is =N-;

m is 1 to 3;

n is 1 to 4;

D is -N(R^5)-C(Z)- (where Z is oxygen, sulfur or H$_2$, and R^5 is hydrogen or alkyl);

E is -C(Z)-N(R^5)- (where Z is oxygen, sulfur or H$_2$, R^5 is hydrogen or alkyl, and the nitrogen is attached to the pyridinyl ring);

R^1 is halo or haloalkyl;

R^2 is -N(R^{10})R^{11}, -O-R^8-S(O)$_p$-R^9 (where p is 0), -O-R^8-C(O)OR^5, -O-(R^8-O)$_t$-R^5 (where t is 1) or -O-R^8-N(R^{10})R^{11} where:

each R^5 is independently hydrogen or alkyl;

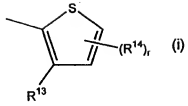
each R^8 is independently a straight or branched alkylene chain;

R^9 is alkyl; and

R^{10} and R^{11} are each independently hydrogen, alkyl, or -R^8-O-R^5 (where R^8 is a straight or branched alkylene chain and R^5 is hydrogen or alkyl);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to one additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by alkyl;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen; and

R^{10} and R^{11} together with the nitrogen to which they are attached form piperazinyl optionally substituted by one or more substituents selected from the group consisting of alkyl and $-C(O)R^5$; and

R^4 is hydrogen or halo.

Of this group of compounds, a preferred subgroup of compounds are those compounds wherein:

m is 1;

n is 1;

D is -N(H)-C(O)-;

E is -C(O)-N(H)- (where the nitrogen is bonded to the 2-position of the pyridinyl ring);

R^1 is halo in the 5-position;

R^2 is $-N(R^{10})R^{11}$, $-O-R^8-S(O)_p-R^9$ (where p is 0), $-O-R^8-C(O)OR^5$, $-O-(R^8-O)_t-R^5$ (where t is 1) or $-O-R^8-N(R^{10})R^{11}$ where:

each R^5 is independently hydrogen, methyl or ethyl;

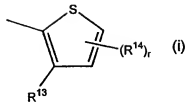
each R^8 is independently a methylene, ethylene or propylene chain;

R^9 is methyl or ethyl; and

R^{10} and R^{11} are each independently hydrogen, methyl, ethyl, or $-R^8-O-R^5$ (where R^8 is ethylene and R^5 is hydrogen, methyl or ethyl); or

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to one additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by alkyl;

R^3 is a radical of the formula (i):



where r is 1;

R^{13} is chloro; and

R^{14} is in the 4-position and is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen; and

R^{10} and R^{11} together with the nitrogen to which they are attached form piperazinyl optionally substituted by methyl or ethyl; and

R^4 is hydrogen, bromo or chloro in the 5-position.

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein:

R^1 is chloro;

R^2 is $-O-R^8-S(O)_p-R^9$ (where p is 0), $-O-R^8-C(O)OR^5$ or $-O-(R^6-O)_t-R^6$ (where t is 1 or 2) where:

each R^5 is independently hydrogen, methyl or ethyl;

each R^8 is independently a methylene, ethylene or propylene chain; and

R^9 is methyl or ethyl.

Of this class of compounds, more preferred compounds are those compounds selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(methylthio)methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(ethoxycarbonyl)methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-ethoxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide, and

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(2-methoxyethoxy)ethoxy)-5-chlorobenzamide.

Of this subgroup of compounds, another preferred class of compounds are those compounds wherein:

R^1 is chloro; and

R^2 is $-N(R^{10})R^{11}$ or $-O-R^8-N(R^{10})R^{11}$ where:

R^8 is a methylene, ethylene or propylene chain; and

R^{10} and R^{11} are each independently hydrogen, methyl, ethyl, or $-R^8-O-R^5$ (where R^8 is ethylene and R^5 is hydrogen, methyl or ethyl).

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(*N*'-methyl-*N*'-(2-hydroxyethyl)amino)propoxy)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-amino-5-chlorobenzamide.

Of this subgroup of compounds, another preferred class of compounds are those compounds wherein:

R^1 is chloro;

R^2 is $-N(R^{10})R^{11}$ or $-O-R^8-N(R^{10})R^{11}$ where:

R^8 is methylene, ethylene or propylene; and

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to one additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by alkyl and is selected from the group consisting of morpholinyl, piperazinyl, pyrrolidinyl or imidazolyl.

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-morpholinylpropoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(pyrrolidin-1-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(pyrrolidin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(imidazol-1-yl)propoxy)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide.

Of the compounds of formula (I) described above, another preferred group of compounds are those compounds of formula (I) wherein:

A is =N-;

m is 1 to 3;

n is 1 to 4;

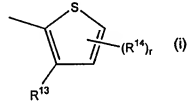
D is -N(R^5)-C(Z)- (where Z is oxygen, sulfur or H_2, and R^5 is hydrogen or alkyl);

E is -C(Z)-N(R^5)- (where Z is oxygen, sulfur or H_2, R^5 is hydrogen or alkyl, and the nitrogen is attached to the pyridinyl ring);

R^1 is halo or haloalkyl;

R^2 is hydrogen, haloalkyl, or -OR^5 where R^5 is hydrogen or alkyl;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, cyano, -R^8-CN, -N(R^{10})R^{11}, -C(R^7)H-N(R^{10})R^{11}, -C(R^7)H-R^8-N(R^{10})R^{11}, -C(R^7)H-$N^{\oplus}$(R^9)(R^{16})$_2$, -C(R^7)H-R^8-$N^{\oplus}$(R^9)(R^{16})$_2$, -C(O)OR^5, -C(R^7)H-C(O)OR^5, -C(R^7)H-R^8-C(O)OR^5, -OR^5, -C(R^7)H-OR^5, -C(R^7)H-R^8-OR^5, -C(R^7)H-O-R^{15}, -S(O)$_p$-R^{15} (where p is 0 to 2), -C(R^7)H-S(O)$_p$-R^{15} (where p is 0 to 2), -C(R^7)H-R^8-S(O)$_p$-R^{15} (where p is 0 to 2), -S(O)$_p$-N(R^5)R^6 (where p is 0 to 2), -C(O)N(R^5)R^6, -C(R^7)H-C(O)N(R^5)R^6, -C(R^7)H-R^8-C(O)N(R^5)R^6, -C(R^7)H-N(R^5)-(R^8-O)$_t$-R^5 (where t is 1 to 6), -C(R^7)H-R^8-N(R^5)-(R^8-O)$_t$-R^5 (where t is 1 to 6), -C(R^7)H-O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -C(R^7)H-R^8-O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -O-R^8-CH(OH)-CH_2-OR^5, -C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5, -C(R^7)H-N(R^5)-R^8-[CH(OH)]$_t$-CH_2-OR^5 (where t is

1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, $-C(NR^{17})-N(R^5)R^8$, $-C(R^7)H-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-O-N(R^5)R^6$, heterocyclyl (wherein the heterocyclyl radical is not attached to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (wherein the heterocyclyl radical is not attached to the alkyl radical through a nitrogen atom and is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$); where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{15})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^5$,

$-R^8$-C(O)OR^5, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8$-OR^5, -C(O)OR^5, -N(R^5)R^6, and -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8$-OR^5, -C(O)OR^5, -N(R^5)R^6, and -C(O)N(R^5)R^6), where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, -C(O)OR^5, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl, where

each R^5 is hydrogen, alkyl, aryl or aralkyl; and

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR^5, or $-NO_2$;

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8$-CN, =N(R^{17}), $-OR^5$, -C(O)OR^5, $-R^8$-C(O)OR^5, -N(R^5)R^6, $-R^8$-N(R^5)R^6, -C(O)N(R^5)R^6, $-R^8$-C(O)N(R^5)R^6, -N(R^5)-N(R^5)R^6, -C(O)R^5, -C(O)-(R^8-O)$_t$-R^5 (where t is 1 to 6), -S(O)$_p$-R^9 (where p is 0 to 2), $-R^8$-S(O)$_p$-R^9 (where p is 0 to 2), -(R^8-O)$_t$-R^5 (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, -C(O)OR^5, -N(R^5)R^6, and -C(O)N(R^5)R^6), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene,

alkylidene or alkylidyne chain;
each R^9 is independently alkyl, aryl or aralkyl;
each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$, where
R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and
each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;
each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), where
R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and
each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain; or
both R^{16}s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6), where
R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and
each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;
each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$, where
R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

and R^4 is hydrogen or halo.

Of this group of compounds, a preferred subgroup of compounds are those compounds wherein:

m is 1;

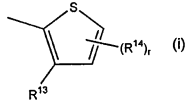
n is 1;

D is -N(H)-C(O)-;

E is -C(O)-N(H)- (where the nitrogen is bonded to the 2-position of the pyridinyl ring);

R^2 is hydrogen, haloalkyl, or $-OR^5$ where R^5 is hydrogen or alkyl;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^6-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^6-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^5)=C(R^{16})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;
each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;
each R^9 is independently alkyl, aryl or aralkyl;
each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^8$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^8$), where
R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and
each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;
or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl, where
each R^5 is hydrogen, alkyl, aryl or aralkyl; and
R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-C(O)OR^5$, or $-NO_2$;
or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2),

$-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$ where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

and R^4 is in the 5-position.

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein:

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{16})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$,

$-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$) where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl, where

each R^8 is independently hydrogen, alkyl, aryl or aralkyl; and

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-C(O)OR^5$, or $-NO_2$.

Of this class of compounds, a preferred subclass of compounds are those compounds wherein:

R^{10} is hydrogen, alkyl, or $-R^8-OR^5$; and

R^{11} is hydrogen, alkyl or $-R^8-OR^5$;

where each R^8 is independently a straight or branched alkylene chain, and each R^5 is hydrogen or alkyl.

Of this subclass of compounds, preferred compounds are those compounds selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N',N'*-di(2-hydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(3-hydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,2-dimethyl-2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-ethoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(amino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((dimethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(1-methylethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(ethylamino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-(diethylamino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of this class of compounds, another preferred subclass of compounds are those compounds wherein:

R^{10} is hydrogen, alkyl, or $-R^8-N(R^5)R^6$, and

R^{11} is $-S(O)_p-R^{15}$ (where p is 0 to 2) or $-R^8-N(R^5)R^6$ where:

R^5 and R^6 are independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain; and

R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or

more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$) where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of this subclass of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(3-(dimethylamino)propyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(methyl)sulfonyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((3,5-dimethylisoxazol-4-yl)sulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((2-(4-hydroxypiperidin-1-yl)ethyl)sulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((dimethylamino)sulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-aminoethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(4-(dimethylamino)but-3-yn-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of this class of compounds, another preferred subclass of compound are those compounds wherein:

R^{10} is hydrogen, alkyl or $-R^8-OR^5$; and

R^{11} is formyl, cyano, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, or $-C(N(R^5)R^5)=C(R^{18})R^{10}$, where:

each R^5 is hydrogen or alkyl;

R^8 is a straight or branched alkylene chain;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^5$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$) where

R^5 and R^8 are independently each hydrogen, alkyl, aryl or aralkyl, and each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain; and

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-C(O)OR^5$, or $-NO_2$.

Of this subclass of compounds, preferred compounds are those compounds selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-ethylureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-carboxyethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-(morpholin-4-yl)ethyl)thioureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(((4-hydroxypiperidin-1-yl)methyl)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-hydroxyethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N'*-methylureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-

3-methoxy-5-chlorobenzamide; and
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(2-hydroxyethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-(chloro)ethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-(acetoxy)ethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-(pyrrolidin-1-yl)ethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N''*-(2-(chloro)ethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-(((2-hydroxyphenyl)carbonyl)oxy)ethyl)ureido)-methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-cyanoamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(2-((fluoromethylcarbonyl)amino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((2-aminoethoxy)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((methylthio)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-ethyl-*N'*-((phenylthio)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-nitro-1-(methylamino)ethenyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-(((2-dimethylphosphoramidoethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the class of compounds, another preferred subclass of compounds are those compounds wherein:

R^{10} is hydrogen, alkyl, haloalkyl, or $-R^8-OR^5$;

R^{11} is cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^6$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl,

aralkyl, halo, haloalkyl, oxo, -OR^5, -R^8-OR^5, -$C(O)OR^5$, -$S(O)_p$-R^9 (where p is 0 to 2), -R^8-$S(O)_p$-R^9 (where p is 0 to 2), -$N(R^5)R^6$ and -$C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R^8-O-$C(O)$-R^5, -R^8-OR^5, -$N(R^5)R^6$, -R^8-$N(R^5)R^6$, -R^8-$C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -R^8-OR^5, -$C(O)OR^5$, -$N(R^5)R^6$, and -$C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -R^8-OR^5, -$C(O)OR^5$, -$N(R^5)R^6$, and -$C(O)N(R^5)R^6$) where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of this subclass of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-(morpholin-4-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(4-hydroxycyclohexyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(pyridin-2-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(thiazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(thiazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(4-(oxo)oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(pyridin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(dihydro-4(*H*)-1,3-oxazin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(*t*-butyl)-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-(((thiazol-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-methoxyethyl)-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(oxazol-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(4-trifluoromethyl-5-(methoxycarbonyl)pyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(dihydro-4(*H*)-1,3-oxazin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(5-methyloxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(tetrazol-5-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(tetrazol-5-yl)amino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(4-methyloxazolin-2-yl)amino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(pyrazol-3-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(2,2,2-trifluoroethyl)-*N'*-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(4-(ethoxycarbonyl)oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(3,4-dihydro-2*H*-pyrrol-5-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(1,2,4-triazol-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(3,4-dihydro-2*H*-pyrrol-5-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(pyridin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-amino-6-methylpyrimidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((1,2,4-oxadiazol-3-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(2-(imidazol-4-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(3,4,5,6-tetrahydropyridin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-chloropyrimidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-ethyl-*N'*-((imidazol-2-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(4-aminopyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(4-aminopyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(4-(methylamino)pyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((3-((methylthio)methyl)-1,2,4-oxadiazol-5-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-

chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(1,3,2-dioxaphospholan-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the subgroup of compounds, another preferred class of compounds are those compounds wherein:

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$ where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of this class of compounds, a preferred subclass of compounds are those compounds wherein the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, and nitro.

Of this subclass of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((4,5-dihydropyrazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((morpholin-4-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((pyrazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((hydantoin-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((1,4,5,6-tetrahydropyrimidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((pyrrolidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2,3,4,5,6,7-hexahydro-3,7-dimethyl-2,6-dioxo-1*H*-purin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(pyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(5-bromopyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((5-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-methylimidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2,4-dimethylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2,5-dimethylimidazol-1-yl)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-methyl-4-nitroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4,5-dichloroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(chloromethyl)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((2-(fluoromethyl)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the class of compounds, another preferred subclass of compounds are those compounds wherein the *N*-heterocylic ring is substituted by one or more substituents selected from the group consisting of alkyl, nitro, $-R^8$-CN, $-OR^5$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl.

Of this subclass of compounds, preferred compounds are those compounds selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((4-(hydroxymethyl)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((5-(hydroxymethyl)imidazol-1-yl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(methoxymethyl)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(hydroxymethyl)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-formylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(*N'*-amino-*N'*-methylamino)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-hydroxypiperidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(methylthio)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-methyl-4-nitroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(cyanomethyl)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the class of compounds, another preferred subclass of compounds are those compounds wherein the *N*-heterocylic ring is substituted by one or more substituents selected from the group consisting of alkyl, oxo, $=N(R^{17})$, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-(R^8-O)_f-R^5$, and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, or $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, $-R^8-C(O)-N(R^5)R^6$ where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of this subclass of compounds, preferred compounds are those wherein the *N*-heterocylic ring is substituted by $=N(R^{17})$ and is optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, and $-(R^8-O)_f-R^5$, where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$ where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of these compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5,5-(dimethyl)tetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-ethylimino-5,5-(dimethyl)tetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5(*S*)-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5(*R*)-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-iminotetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5-(methoxymethyl)tetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-4-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*trans*-4,5-dimethyl-2-iminotetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*cis*-4,5-dimethyl-2-iminotetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((3-methyl-2-imino-2,3-dihydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-tetrahydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-1,2-dihydropyrimidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-4-(hydroxymethyl)tetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-iminotetrahydrothiazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-4-oxoimidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((tetrahydro-2-imino-2*H*-pyrimidin-1-ylpyrimidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(methoxycarbonylamino)imidazolin-1-yl)methyl)-3-

chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(cyanoimino)tetrahydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-3-((phenylamino)carbonyl)tetrahydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*cis*-4,5-dimethoxy-2-iminotetrahydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-amino-4-imino-1,4-dihydropyrimidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-((2-hydroxyethyl)imino)tetrahydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-iminopiperidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((4-imino-1(4*H*)-pyridinyl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-1(2*H*)-pyridin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(ethylimino)pyrrolidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and
N-(5-chloropyridin-2-yl)-2-[((4-((2-(((aminocarbonyl)methyl)imino)tetrahydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the class of compounds, another preferred subclass of compounds are those compounds wherein the *N*-heterocylic ring is substituted by $-N(R^5)R^6$ and optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, $-N(R^5)R^6$, $-OR^5$, and $-C(O)N(R^5)R^6$, where R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl.

Of this subclass of compounds, preferred compounds are selected from the group consisting of:
N-(5-chloropyridin-2-yl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((5-aminotetrazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((3-amino-1,2,4-triazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((3,5-diamino-4*H*-1,2,4-triazol-4-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-amino-5-(aminocarbonyl)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2,6-diaminopurin-9-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2,6-diaminopurin-7-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((5-amino-2-oxo-2*H*-pyrimidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((6-aminopurin-9-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((6-aminopurin-7-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-amino-6-oxopurin-9-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-amino-6-oxopurin-7-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((5-(dimethylamino)-1,2,4-oxadiazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((5-amino-1,2,4-oxadiazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(methylamino)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2,4-diamino-6-hydroxypyrimidin-5-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(ethylamino)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(1-methylethyl)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((3-dimethylamino-5-methylpyrazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and
N-(5-chloropyridin-2-yl)-2-[((4-((3-dimethylamino-5-methylpyrazol-2-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the group of compounds described above, another preferred subgroup of compounds are those compounds wherein:

each R^{14} is independently alkyl, -R^8-CN, -C(R^7)H-R^8-N(R^{10})R^{11}, -C(R^7)H-R^8-$N^{\oplus}$(R^9)(R^{16})$_2$, -C(R^7)H-OR^5, -C(R^7)H-R^8-OR^5, -C(R^7)H-O-R^{15}, -C(R^7)H-S(O)$_p$-R^{15} (where p is 0 to 2), -C(R^7)H-N(R^5)-(R^8-O)$_t$-R^5 (where t is 1 to 6), -C(R^7)H-N(R^5)-R^8-[CH(OH)]$_t$-CH_2-OR^5 (where t is 1 to 6), -C(R^7)H-N(R^5)-S(O)$_2$-N(R^{10})R^{11}, -C(R^7)H-O-N(R^5)R^6, or heterocyclyl (wherein the heterocyclyl radical is not attached to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR^5, -C(O)OR^5, -N(R^5)R^6 or -C(O)N(R^5)R^6), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, -R^8-CN, -OR^5, -R^8-OR^5, -S(O)$_p$-R^{15} (where p is 0 to 2), -R^8-S(O)$_p$-R^{15} (where p is 0 to 2), -N(R^5)R^6, -R^8-N(R^5)R^6, -R^8-C(O)OR^5, -C(O)-R^{15}, -C(O)NH_2, -R^8-C(O)NH_2, -C(S)NH_2, -C(O)-S-R^5, -C(O)-N(R^5)R^{15}, -R^8-C(O)-N(R^5)R^{15}, -C(S)-N(R^5)R^{15}, -R^8-N(R^5)-C(O)H, -R^8-N(R^5)-C(O)R^{15}, -C(O)O-R^8-N(R^5)R^8, -C(N(R^5)R^6)=C(R^{16})R^{10}, -R^8-N(R^5)-P(O)(OR^5)$_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR^5), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR^5, -R^8-OR^5, -C(O)OR^5, -S(O)$_p$-R^9 (where p is 0 to 2), -R^8-S(O)$_p$-R^9 (where p is 0 to 2), -N(R^5)R^8 or -C(O)N(R^5)R^6), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR^5, -R^8-OR^5, -C(O)OR^5, -S(O)$_p$-R^9 (where p is 0 to 2), -R^8-S(O)$_p$-R^9 (where p is 0 to 2), -N(R^5)R^6 and -C(O)N(R^5)R^6), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R^8-O-C(O)-R^5, -R^8-OR^5, -N(R^5)R^6, -R^8-N(R^5)R^6, -R^8-C(O)OR^5, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of

alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -R^8-OR^5, -$C(O)OR^5$, -$N(R^5)R^6$, and -$C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -R^8-OR^5, -$C(O)OR^5$, -$N(R^5)R^6$, and -$C(O)N(R^5)R^6$), where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, -OR^5, -$C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl, where

each R^5 is hydrogen, alkyl, aryl or aralkyl; and

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, -$C(O)OR^5$, or -NO_2;

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, -R^8-CN, =$N(R^{17})$, -OR^5, -$C(O)OR^5$, -R^8-$C(O)OR^5$, -$N(R^5)R^6$, -R^8-$N(R^5)R^6$, -$C(O)N(R^5)R^6$, -R^8-$C(O)N(R^5)R^6$, -$N(R^5)$-$N(R^5)R^6$, -$C(O)R^5$, -$C(O)$-$(R^8$-$O)_t$-R^5 (where t is 1 to 6), -$S(O)_p$-R^9 (where p is 0 to 2), -R^8-$S(O)_p$-R^9 (where p is 0 to 2), -$(R^8$-$O)_t$-R^5 (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR^5, -$C(O)OR^5$, -$N(R^5)R^6$, and -$C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$, where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^8$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain; or

both R^{16}s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6), where

R^5 and R^8 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^9 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of this subgroup of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((pyridinium-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide,

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(hydroxyethoxy)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((methylsulfinyl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-hydroxyethyl)sulfinyl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((pyridinium-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-cyanomethyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(2-methylaminoethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(hydroxy)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((imidazol-2-yl)thio)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((imidazolin-2-yl)thio)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((5-hydroxymethyl-1-methylimidazol-2-yl)thio)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((diethylamino)oxy)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-(imidazolin-2-yl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the group of comounds described above, another preferred subgroup of compounds are those compounds wherein:

each R^{14} is independently $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, or $-C(R^7)H-C(NR^{17})-N(R^5)R^6$, where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$

(where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{16})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected

from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl, where

each R^5 is hydrogen, alkyl, aryl or aralkyl; and

R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-C(O)OR^5$, or $-NO_2$;

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8$-CN, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8$-$C(O)OR^5$, $-N(R^5)R^6$, $-R^8$-$N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8$-$C(O)N(R^5)R^6$, $-N(R^5)$-$N(R^5)R^6$, $-C(O)R^5$, $-C(O)$-$(R^8$-$O)_t$-R^5 (where t is 1 to 6), $-S(O)_p$-R^9 (where p is 0 to 2), $-R^8$-$S(O)_p$-R^9 (where p is 0 to 2), $-(R^8$-$O)_t$-R^5 (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), where

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8$-OR^5, $-C(O)OR^5$, $-R^8$-$C(O)OR^5$, $-C(O)$-$N(R^5)R^6$, or $-R^8$-$C(O)$-$N(R^5)R^6$, where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8$-OR^5, $-C(O)OR^5$, $-R^8$-$C(O)OR^5$, $-C(O)$-$N(R^5)R^6$, or $-R^8$-$C(O)$-$N(R^5)R^6$, where

R^5 and R^6 are independently each hydrogen, alkyl, aryl or aralkyl, and

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain.

Of this subgroup of compounds, preferred compounds are selected from the group

consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-(((amidino)(methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(1-iminoethyl)-*N'*-methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N',N''*-dimethyl-*N'''*-cyanoguanidino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N'*-methyl-*N''*-hydroxyguanidino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N'*-methyl-*N''*-(2-aminoethyl)-*N'''*-cyanoguanidino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N'*-methyl-*N''*-aminoguanidino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N',N''*-dimethyl-*N'''*-(aminocarbonyl)guanidino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(imino(phenyl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(1-imino-2-(aminocarbonyl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(1-imino-4,4,4-trifluorobutyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(imino(pyridin-4-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(imino(thiophen-2-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(imino(pyrazin-2-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(cyclopropyl(imino)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-ethyl-*N'*-(3-cyano-1-iminopropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(1-imino-4,4,4-trifluorobutyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-(2-amino-2-(hydroxyimino)ethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the compounds of formula (I) described above, another preferred group of compounds are those compounds of formula (I) wherein:

A is =N-;

m is 1;

n is 1;

D is -N(H)-C(O)-;

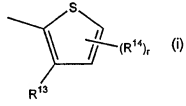
E is -C(O)-N(H)- (where the nitrogen is bonded to the 2-position of the pyridinyl ring);

R^2 is $-N(R^{10})R^{11}$ where:

R^{10} and R^{11} are each independently hydrogen, alkyl or $-R^8-O-R^5$ where R^8 is an alkylene chain, and R^5 is hydrogen or alkyl; or

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl and $-C(O)OR^5$ where R^5 is hydrogen or alkyl;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ or $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 3)

where:

each R^5 is independently hydrogen or alkyl;

R^7 is hydrogen;

R^8 is a straight or branched alkylene chain;

R^{10} and R^{11} are each independently hydrogen, alkyl, formyl, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by $-OR^5$), heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), where:

each R^5 and R^6 is independently hydrogen or alkyl;
each R^8 is independently a straight or branched alkylene chain; and
each R^{15} is alkyl, $-R^8-OR^5$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by $-R^8-OR^5$), or heterocyclylalkyl (optionally substituted by $-OR^5$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, $=N(R^{17})$, $-OR^5$, $-R^8-OR^5$, and $-N(R^5)R^6$; where
each R^5 and R^6 is independently hydrogen or alkyl;
R^8 is a straight or branched alkylene chain; and
each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$;

and R^4 is in the 5-position and is hydrogen or halo.

Of this group of compound, a preferred subgroup of compounds are those compounds wherein:

R^2 is $-N(R^{10})R^{11}$ where:

R^{10} and R^{11} are each independently hydrogen, alkyl or $-R^8-O-R^5$ where R^8 is an alkylene chain, and R^5 is hydrogen or alkyl.

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein:

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen;

R^{10} and R^{11} are each independently hydrogen, alkyl, formyl, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by $-OR^5$), heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$); where:
each R^5 and R^6 is hydrogen or alkyl;
each R^8 is independently a straight or branched alkylene chain; and
each R^{15} is alkyl, $-R^8-OR^5$, $-R^8-C(O)OR^5$, heterocyclyl (optionally

substituted by -R^8-OR^5), or heterocyclylalkyl (optionally substituted by -OR^5);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, =N(R^{17}), -OR^5, -R^8-OR^5, and -N(R^5)R^6; where:

each R^5 is hydrogen or alkyl;

R^8 is straight or branched alkylene chain; and

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR^5, -R^8-OR^5, -C(O)OR^5, -R^8-C(O)OR^5, -C(O)-N(R^5)R^6, or -R^8-C(O)-N(R^5)R^8.

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(3-(dimethylamino)propyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(di(2-methoxyethyl)amino)-5-chlorobenzamide.

Of this group of compounds, another preferred subgroup of compounds are those compounds wherein:

R^2 is -N(R^{10})R^{11} where:

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl and -C(O)OR^5 where R^5 is hydrogen or alkyl.

Of this subgroup of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-(morpholin-4-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(3-(dimethylamino)propyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-methoxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methylsulfonyl-*N'*-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N''*-methyl-*N'*-(2-(pyrrolidin-1-yl)ethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(pyrrolidin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(1-methylethyl)-*N'*-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-(ethoxycarbonyl)piperidin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-(carboxy)piperidin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-ethylureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-ethylpiperazin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-ethyl-*N'*-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(4-trifluoromethyl-5-(methoxycarbonyl)pyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(4-trifluoromethyl-5-carboxypyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((2-iminotetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(tetrazol-5-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide.

Of the compounds of formula (I) described above, another preferred group of compounds are those compounds of formula (I) wherein:

A is =N-;

m is 1;

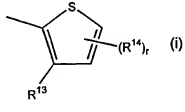
n is 1;

D is -N(H)-C(O)-;

E is -C(O)-N(H)- (where the nitrogen is bonded to the 2-position of the pyridinyl ring);

R^2 is $-O-(R^8-O)_t-R^5$ (where t is 1 to 3) or $-O-(R^8-O)_t-R^{19}$ where R^5 is hydrogen or alkyl, each R^8 is independently a straight or branched alkylene chain, and R^{19} is heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, or haloalkyl);

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen;

R^{10} and R^{11} are each independently hydrogen, alkyl, formyl, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by $-OR^5$), heterocyclyl (optionally substituted by one or more

substituents selected from the group consisting of alkyl, haloalkyl, oxo, -OR^5, and -$C(O)OR^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, -OR^5, and -$C(O)OR^5$); where:

each R^5 and R^6 is hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain; and

each R^{15} is alkyl, -R^8-OR^5, -R^8-$C(O)OR^5$, heterocyclyl (optionally substituted by -R^8-OR^5), or heterocyclylalkyl (optionally substituted by -OR^5);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, =$N(R^{17})$, -OR^5, -R^8-OR^5, and -$N(R^5)R^6$; where

each R^5 is hydrogen or alkyl;

R^8 is straight or branched alkylene chain; and

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR^5, -R^8-OR^5, -$C(O)OR^5$, -R^8-$C(O)OR^5$, -C(O)-$N(R^5)R^6$, or -R^8-C(O)-$N(R^5)R^6$; and

R^4 is in the 5-position and is hydrogen or halo.

Of this group of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide,

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide,

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide,

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-((2-(2-methoxyethoxy)ethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-((2-(2-methoxyethoxy)ethoxy)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(pyridin-3-yloxy)propoxy)-5-chlorobenzamide.

Of the compounds of formula (I) described above, another preferred group of compounds are those compounds of formula (I) wherein:

A is =N-;

m is 1;

n is 1;

D is -N(H)-C(O)-;

E is -C(O)-N(H)- (where the nitrogen is bonded to the 2-position of the pyridinyl ring);

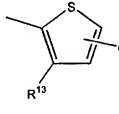
R^2 is -O-R^8-N(R^{10})R^{11} where:

R^8 is a straight or branched alkylene chain; and

R^{10} and R^{11} are each independently hydrogen, alkyl or -R^8-O-R^5 where R^8 is an alkylene chain, and R^5 is hydrogen or alkyl; or

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl and -C(O)OR^5 where R^5 is hydrogen or alkyl;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is -C(R^7)H-N(R^{10})R^{11} where:

R^7 is hydrogen;

R^{10} and R^{11} are each independently hydrogen, alkyl, formyl, -R^8-OR^5, -S(O)$_p$-R^{15} (where p is 0 to 2), -R^8-N(R^5)R^6, -R^8-C(O)OR^5, -C(O)-R^{15}, -C(O)NH_2,

$-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by $-OR^5$), heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), where:

each R^5 and R^6 is hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain; and

each R^{15} is alkyl, $-R^8-OR^5$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by $-R^8-OR^5$), or heterocyclylalkyl (optionally substituted by $-OR^5$); and

R^4 is in the 5-position and is hydrogen or halo.

Of this group of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(morpholin-4-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(pyrrolidin-1-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(morpholin-4-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(imidazol-1-yl)ethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(imidazol-1-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(pyrrolidin-1-yl)ethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(imidazol-1-yl)ethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(pyrrolidin-1-yl)ethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(4-ethylpiperazin-1-yl)propoxy)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-aminoethoxy)-5-chlorobenzamide.

Of the compounds of formula (I) described above, another preferred group of

compounds are those compounds of formula (I) wherein:

A is =N-;

m is 1;

n is 1;

D is -N(H)-C(O)-;

E is -C(O)-N(H)- (where the nitrogen is bonded to the 2-position of the pyridinyl ring);

R^2 is $-O-R^8-O-C(O)R^5$, $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$, or $-O-R^8-CH(OH)-CH_2-OR^5$ where

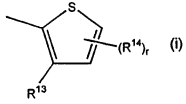
each R^5 is hydrogen or alkyl;

R^8 is a straight or branched alkylene chain; and

R^{10} and R^{11} are each independently hydrogen, alkyl or $-R^8-O-R^5$ where R^8 is an alkylene chain, and R^5 is hydrogen or alkyl; or

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl and $-C(O)OR^5$ where R^5 is hydrogen or alkyl;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ or $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$ where:

R^5 is hydrogen or alkyl;

R^7 is hydrogen;

R^{10} and R^{11} are each independently hydrogen, alkyl, formyl, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by $-OR^5$), heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$); where:

each R^5 and R^6 is hydrogen or alkyl;

each R^6 is independently a straight or branched alkylene chain; and each R^{15} is alkyl, $-R^6-OR^5$, $-R^6-C(O)OR^5$, heterocyclyl (optionally substituted by $-R^6-OR^5$), or heterocyclylalkyl (optionally substituted by $-OR^5$); and

R^4 is in the 5-position and is hydrogen or halo.

Of this group of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-acetoxyethoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((dimethylamino)sulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxy-3-(imidazol-1-yl)propoxy)-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxy-3-methoxypropoxy)-5-chlorobenzamide.

Of the compounds of formula (I) described above, another preferred group of compounds are those compounds of formula (I) wherein:

A is =N-;

m is 1 to 3;

n is 1;

D is $-N(R^5)-C(Z)-$ (where Z is oxygen and R^5 is hydrogen or alkyl);

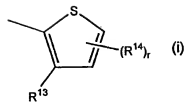
E is $-C(Z)-N(R^5)-$ (where Z is oxygen, R^5 is hydrogen or alkyl, and the nitrogen is attached to the pyridinyl ring);

each R^1 is independently hydrogen, halo or $-OR^5$;

or two adjacent R^1's together with the carbons to which they are attached form a dioxole ring fused to the phenyl ring wherein the dioxole ring is optionally substituted by alkyl;

R^2 is hydrogen;

R^3 is a radical of the formula (i):



(i)

where r is 1;

R^{13} is halo; and

R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen; and

R^{10} and R^{11} are each independently hydrogen, alkyl, formyl, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by $-OR^5$), heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, oxo, $-OR^5$, and $-C(O)OR^5$); where:

each R^5 and R^6 is hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain; and

each R^{15} is alkyl, $-R^8-OR^5$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by $-R^8-OR^5$), or heterocyclylalkyl (optionally substituted by $-OR^5$); and

R^4 is in the 5-position and is hydrogen or halo.

Of this group of compounds, preferred compounds are selected from the group consisting of:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3,4,5-trimethoxybenzamide;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-((*N*'-methyl-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole; and

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-((*N*'-(2-methoxyethyl)-*N*'-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole.

Of the compounds of formula (I) described above, another preferred group of

compounds are those compounds of formula (I) wherein:

A is -CH-;

m is 1;

n is 1;

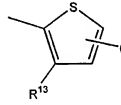
D is -N(R^5)-C(Z)- (where Z is oxygen and R^5 is hydrogen or alkyl);

E is -C(Z)-N(R^5)- (where Z is oxygen, R^5 is hydrogen or alkyl, and the nitrogen is attached to the phenyl ring having the R^4 substituent);

R^1 is alkyl or halo;

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR^5, -$S(O)_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -C(O)N(R^5)R^6, -N(R^{10})R^{11}, -C(R^7)H-OR^5, -C(R^7)H-$S(O)_p$-R^9 (where p is 0 to 2), -O-R^8-$S(O)_p$-R^9 (where p is 0 to 2), -C(R^7)H-N(R^5)R^6, -O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}, -O-R^8-N(R^{10})R^{11}, -O-R^8-O-C(O)R^5, -O-R^8-CH(OH)-CH_2-OR^5; O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -O-R^8-C(O)R^5, -O-R^8-C(O)OR^5, -N(R^5)-R^8-N(R^{10})R^{11}, -$S(O)_p$-R^8-N(R^5)R^6 (where p is 0 to 2), -$S(O)_p$-R^8-C(O)OR^5 (where p is 0 to 2), -N(R^5)-CH(R^{12})-C(O)OR^5;

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is hydrogen, alkyl, halo, haloalkyl, -N(R^5)R^6, -C(R^7)H-N(R^5)R^8, -OR^5, -$S(O)_p$-R^8-N(R^5)R^6 (where p is 0 to 2) or heterocyclylalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, -N(R^{10})R^{11}, -C(R^7)H-N(R^{10})R^{11}, -C(R^7)H-N$^{\oplus}$(R^9)(R^{16})$_2$, -N(R^5)-R^8-C(O)OR^5, -C(R^7)H-N(R^5)-R^8-C(O)OR^5, -C(O)OR^5, -OR^5, -C(R^7)H-OR^5, -$S(O)_p$-R^{15} (where p is 0 to 2), -C(R^7)H-$S(O)_p$-R^{15} (where p is 0 to 2), -$S(O)_p$-N(R^5)R^8 (where p is 0 to 2), -C(O)N(R^5)R^6, -C(R^7)H-N(R^5)-(R^8-O)$_t$-R^5 (where t is 1 to 6), -C(R^7)H-O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -O-R^8-CH(OH)-CH_2-OR^5, -C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5, -C(R^7)H-N(R^5)-R^8-[CH(OH)]$_t$-CH_2-OR^5 (where t is 1 to 6), -C(R^7)H-N(R^5)-$S(O)_2$-N(R^{10})R^{11}, -C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}, or

$-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$;

R^4 is halo;

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

R^7 is hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene or alkylidene chain;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, aryl, aralkyl, formyl, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, oxo, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6);

R^{12} is a side chain of an α-amino acid;

each R^{16} is independently alkyl, haloalkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl; and

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one

or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), or

both R^{9}'s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6).

Of this group of compounds, a preferred subgroup of compounds are those compounds wherein:

D is -N(H)-C(O)-;

E is -C(O)-N(H)-;

R^1 is halo;

R^2 is hydrogen, $-OR^5$, $-N(R^{10})R^{11}$, $-O-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-O-R^8-N(R^{10})R^{11}$, $-O-R^8-O-C(O)R^5$ or $-O-R^8-C(O)OR^5$ where:

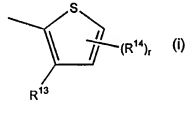
each R^5 is hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain;

R^9 is alkyl;

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms;

R^3 is a radical of formula (i):



(i)

where:

r is 1;

R^{13} is halo; and

R^{14} is in the 4-position and is $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen or alkyl; and

R^{10} and R^{11} are each independently hydrogen, alkyl, $-R^8-OR^5$ or heterocyclyl; or R^{10} and R^{11} together with the nitrogen to which they are attached form a piperazine ring optionally substituted by alkyl; and

R^4 is chloro.

Of this subgroup of compounds, preferred compounds are selected from the group consisting of:

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-fluorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(ethoxycarbonyl)methoxy-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-((acetoxy)ethoxy)-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(morpholin-4-yl)ethoxy)-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-((methylthio)methoxy)-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(3-(morpholin-4-yl)propoxy)-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((*N'*-methyl-*N'*-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide; and

N-(4-chlorophenyl)-2-[((4-((*N'*-methyl-*N'*-(oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of the group of compounds described above, another preferred subgroup of compounds are those compounds wherein:

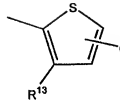
D is -N(H)-C(O)-;

E is -C(O)-N(H)-;

R^1 is methyl or chloro;

R^2 is hydrogen or -OR^5;

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is alkyl, halo, OR^5 (where R^5 is alkyl) or heterocyclylalkyl (where the heterocyclic ring is optionally substituted by alkyl); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, $-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-N^{\oplus}(R^9)(R^{16})_2$, $-C(O)OR^5$, $-C(R^7)H-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, or $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6);

R^4 is halo;

R^5 and R^6 are each independently hydrogen or alkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain;

R^9 is alkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, aryl, aralkyl, formyl, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^5$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, $-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)R^5$, and $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6);

R^{15} is alkyl, haloalkyl, aryl, aralkyl, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the

group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

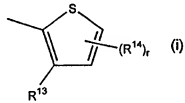
or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl; and

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), or

both R^{16}'s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6).

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein:

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is halo, alkyl or 4-methylpiperazin-1-yl, and

each R^{14} is independently hydrogen or $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen or alkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, aryl, aralkyl, formyl, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, heterocyclyl (optionally substituted by

alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$) where:

each R^5 and R^6 are independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain; and

each R^{15} is alkyl, haloalkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocydylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$).

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(4-chlorophenyl)-2-[((3-methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-((4-methylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((5-((dimethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N'*-methyl-*N'*-(ethoxycarbonylmethyl)amino)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N'*-methyl-*N'*-(carboxymethyl)amino)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N',N'*-di(2-hydroxyethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((*N'*-(3-dimethylaminophenyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

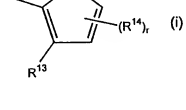
N-(4-chlorophenyl)-2-[((3-chloro-4,5-di((*n*-propyl)aminomethyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((*N'*-methyl-*N'*-(2-dimethylaminoethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(ethoxycarbonylmethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2-dimethylaminoethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(3-(imidazol-1-yl)propyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(3-(dimethylamino)propyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(2-methylpropyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(1-methylpiperidin-4-yl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(2-(morpholin-4-yl)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-hydroxyamino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2-diethylaminoethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(2-hydroxyethyl)l-*N'*-(2-(morpholin-4-yl)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; and
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide.

Of the subgroup of compounds described above, another preferred class of compounds are those compounds wherein:

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is halo or alkyl, and

each R^{14} is independently hydrogen, alkyl or $-C(R^7)H-N(R^{10})R^{11}$ where:

R^7 is hydrogen or alkyl; and

R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, oxo, $-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)R^5$, and $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6) where

each R^5 is hydrogen or alkyl; and

R^8 is a straight or branched alkylene chain.

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(4-chlorophenyl)-2-[((4-methyl-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((4-(carboxymethyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((5-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((4-(ethoxycarbonylmethyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(thiomorpholin-4-yl)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(morpholin-4-yl)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(1-(oxo)thiomorpholin-4-yl)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((4-(((2-(2-methoxyethoxy)ethoxy)methyl)carbonyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-(morpholin-4-yl)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(1,1,4-tri(oxo)thiomorpholin-4-yl)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-(thiomorpholin-4-yl)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((imidazol-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-methyl-4-((4-methylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-methyl-5-((4-methylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4*H*-1,2,4-triazol-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((imidazol-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((tetrazol-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((tetrazol-2-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((pyrazol-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((1,2,3-triazol-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((1,2,3-triazol-2-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4-ethylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

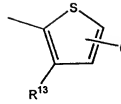
N-(4-chlorophenyl)-2-[((3-chloro-4-((4-oxomorpholin-4-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4-acetylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; and

N-(4-chlorophenyl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Of this subgroup of compounds described above, another preferred class of compounds are those compounds wherein:

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is halo or alkyl, and

each R^{14} is independently $-C(R^7)H-S(O)_p-R^{15}$ where:

p is 0 to 2;

R^7 is hydrogen or alkyl; and

R^{15} is alkyl, $-R^8-N(R^5)R^8$ or $-R^8-C(O)OR^5$ where:

R^5 and R^8 are each independently hydrogen or alkyl; and

each R^8 is independently a straight or branched alkylene chain.

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(4-chlorophenyl)-2-[((3-chloro-5-((methylthio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((methoxycarbonylmethyl)thio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((methoxycarbonylmethyl)sulfinyl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((methylsulfinyl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((carboxymethyl)thio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((methylsulfonyl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((2-(dimethylamino)ethyl)thio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((2-(dimethylamino)ethyl)sulfinyl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((methylthio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-(((methoxycarbonylmethyl)thio)methyl)thiophen-2-

yl)carbonyl)amino]-5-chlorobenzamide;

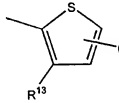
N-(4-chlorophenyl)-2-[((3-chloro-4-(((2-(dimethylamino)ethyl)thio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((methylsulfonyl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; and

N-(4-chlorophenyl)-2-[((3-chloro-4-((methylsulfinyl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide.

Of the subgroup of compounds described above, another preferred class of compounds are those compounds wherein:

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is halo or alkyl, and

each R^{14} is independently formyl, $-N(R^{10})R^{11}$, $-C(O)OR^5$, $-C(R^7)H\text{-}OR^5$ or $-C(O)N(R^5)R^6$ where:

R^5 and R^6 are each independently hydrogen or alkyl;

R^7 is hydrogen or alkyl; and

R^{10} and R^{11} are independently hydrogen or alkyl.

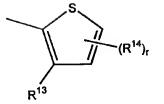
Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(4-chlorophenyl)-2-[((3-chloro-5-carboxythiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; and

N-(4-chlorophenyl)-2-[((3-chloro-4-(hydroxymethyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide.

Of the subgroup of compounds described above, another preferred class of compounds are those compounds wherein:

R^3 is a radical of formula (i):



(i)

where:

r is 1 or 2;

R^{13} is alkyl, halo or $-OR^5$ (where R^5 is alkyl), and

each R^{14} is independently hydrogen, halo, $-C(R^7)H-N^{\oplus}(R^5)(R^{16})_2$, $-S(O)_p-R^{15}$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, or $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6) where:

R^5 and R^6 are independently hydrogen or alkyl;

R^7 is hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene chain;

R^{10} and R^{11} are independently hydrogen, alkyl or $-R^8-OR^5$ where R^8 is a straight or branched alkylene chain and R^5 is hydrogen or alkyl; and

R^{15} is alkyl or $-N(R^5)R^6$; and

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), or

both R^{16}s together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^6-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6).

Of this class of compounds, preferred compounds are selected from the group consisting of:

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*,*N'*-dimethyl-*N'*-(2-hydroxyethyl)ammonio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((((2-hydroxyethoxy)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((2-(2-methoxyethoxy)ethoxy)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((2-(2-(2-methoxyethoxy)ethoxy)ethoxy)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((2-methoxyethoxy)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*,*N'*-dimethyl-*N'*-(3-hydroxypropyl)ammonio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2,3-dihydroxypropyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2,3,4,5,6-pentahydroxyhexyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2-(hydroxyethoxy)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-(methylsulfonyl)thiophen-2-yl)carbonyl)amino]-5-methylbenzamide;
N-(4-chlorophenyl)-2-[((3-chlorothiophen-2-yl)carbonyl)amino]-5-methylbenzamide;
N-(4-chlorophenyl)-2-[((3-bromothiophen-2-yl)carbonyl)amino]-5-methylbenzamide;
N-(4-chlorophenyl)-2-[((3-chloro-4-((1-methylethyl)sulfonyl)thiophen-2-yl)carbonyl)amino]-5-methylbenzamide;
N-(4-chlorophenyl)-2-[((4-(methylamino)sulfonyl-3-methylthiophen-2-yl)carbonyl)amino]-5-methylbenzamide; and
N-(4-chlorophenyl)-2-[((3-methoxythiophen-2-yl)carbonyl)amino]-5-methylbenzamide.

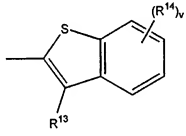
Of the compounds of formula (I) described above, another preferred group of compounds are those compounds of formula (I) wherein:

A is -CH- or =N-;
m is 1 to 3;
n is 1 to 4;
D is -N(H)-C(O)- or -N(H)-CH_2-;
E is -C(O)-N(H)-; (where the nitrogen atom is bonded to the aromatic ring containing the R^4 substituent);

each R^1 is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^5)R^6$, $-O-C(O)R^5$, or $-N(R^5)-CH(R^{12})-C(O)OR^5$;

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-OC(O)-R^5$, $-C(O)N(R^5)R^6$, $-N(R^{10})R^{11}$, $-C(R^7)H-OR^5$, $-C(R^7)H-S(O)_p-R^9$ (where p is 0 to 2), $-O-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-C(R^7)H-N(R^5)R^6$, $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$ $-O-R^6-N(R^{10})R^{11}$, $-O-R^8-O-C(O)R^5$, $-O-R^8-CH(OH)-CH_2-OR^5$; $-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-C(O)R^5$, $-O-R^8-C(O)OR^5$, $-N(R^5)-R^8-N(R^{10})R^{11}$, $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2), $-S(O)_p-R^8-C(O)OR^5$ (where p is 0 to 2), or $-N(R^5)-CH(R^{12})-C(O)OR^5$;

R^3 is a radical of formula (ii):



(ii)

where v is 1 to 4;

R^{13} is hydrogen, alkyl, halo, haloalkyl, $-N(R^5)R^6$, $-C(R^7)H-N(R^5)R^6$, $-OR^5$, $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2) or heterocyclylalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, $-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-N^{\oplus}(R^9)(R^{16})_2$, $-N(R^5)-R^8-C(O)OR^5$, $-C(R^7)H-N(R^5)-R^8-C(O)OR^5$, $-C(O)OR^5$, $-OR^5$, $-C(R^7)H-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-S(O)_p-R^{15}$ (where p is 0 to 2), $-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$, or $-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$;

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, or $-R^8-N(R^5)R^6$;

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene or alkylidene chain;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, aryl, aralkyl, formyl, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, oxo, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^6-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6);

R^{12} is a side chain of an α-amino acid;

R^{15} is alkyl, haloalkyl, aryl, aralkyl, $-R^8-OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$);

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, $-OR^5$, $-C(O)OR^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl; and

each R^{16} is independently alkyl, aryl, aralkyl, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), or

both R^{16}s together with the nitrogen to which they are attached (and wherein the R^5 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), and $-(R^8-O)_t-R^5$ (where t is 1 to 6); and

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-C(O)-N(R^5)R^6$, or $-R^8-C(O)-N(R^5)R^6$.

Of this group of compounds, preferred compounds are selected from the group consisting of:

N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(pyridin-3-yl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(pyridin-2-yl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-methoxyphenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(3-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-bromophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(5-chloropyridin-2-yl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(3-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(3-methylphenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-chloro-2-methylphenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-cyanophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-fluorophenyl)-2-[((benzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-fluorophenyl)-2-[((3-methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-chlorophenyl)-2-[((3-methoxybenzo[*b*]thien-2-yl)carbonyl)amino]-5-methylbenzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]benzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-methoxybenzamide;

N-(4-bromophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-methylbenzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-(pyrrolidin-1-yl)methylbenzamide;

N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-(trifluoromethyl)benzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-

(dimethylamino)methylbenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-(4-methylpiperazin-1-yl)benzamide;
N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-(amino)methylbenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-hydroxybenzamide;
N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4,5-dimethoxybenzamide;
N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4,5-dihydroxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-fluorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-chlorobenzamide;
N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-methoxybenzamide;
N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-hydroxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-fluorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-methoxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-6-fluorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-hydroxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-methylbenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-(ethoxycarbonyl)methoxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4,5-dihydroxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4,5-dimethoxybenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]benzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-aminobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-methyl-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-methylbenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-methyl-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-fluoro-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;
N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4,5-difluorobenzamide;

N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-(*N*'-methyl-*N*'-(3-(dimethylamino)propylamino-5-fluorobenzamide;

N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-(4-methylpiperazin-1-yl)-5-fluorobenzamide;

N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-4-((3-(4-methylpiperazin-1-yl)propyl)amino)-5-fluorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-(dimethylamino)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-(dimethylamino)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-(4-methylpiperazin-1-yl)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-(4-methylpiperazin-1-yl)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-(4-(carboxymethyl)piperazin-1-yl)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-((methoxycarbonyl)methylthio)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-chloro-5-(*N*'-methyl-*N*'-(ethoxycarbonyl)methylamino)benzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)-3-chlorothiophen-2-yl)carbonyl)amino]-3-chloro-5-(*N*'-methyl-*N*'-(ethoxycarbonyl)methylamino)benzamide;

N-phenyl-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-hdyroxy-4-((1,1-dimethylethyl)carbonyl)oxybenzamide; and

N'-(4-chlorophenyl)-2-((3-methylbenzo[*b*]thien-2yl)methyl)amino-5-benzamide.

Of the compounds disclosed above, the following compounds are the most preferred compounds of the invention:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-methoxyethoxy)-5-chlorobenzamide,
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N''*-(2-(pyrrolidin-1-yl)ethyl)ureido)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-(2-methoxyethoxy)ethoxy)-5-chlorobenzamide,
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-5-chlorobenzamide,
N-(5-chloropyridin-2-yl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide,
N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide
N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5(*S*)-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide,
N-(5-chloropyridin-2-yl)-2-[((4-((dimethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-methylimidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(3,4-dihydro-2*H*-pyrrol-5-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((2-(methylamino)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-(imidazolin-2-yl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(pyridin-4-yl)amino)methyl)-3-chlorothiophen-2-

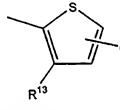
yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; and

N-(5-chloropyridin-2-yl)-2-[((4-((2-(ethylamino)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

Preparation of Compounds of The Invention

It is understood that in the following description, combinations of substituents and/or variables on the depicted formulae are permissible only if such combinations result in stable compounds.

For purposes of illustration only and unless otherwise indicated, the following Reaction Schemes are directed to the preparation of the compounds of the invention as set forth above in the Summary of the Invention as compounds of formula (I). In particular, for purposes of illustration only and unless otherwise indicated, the compounds prepared in the following Reaction Schemes are compounds of formula (I) wherein D is -N(R^5)-C(O)- (where the nitrogen is bonded to the phenyl ring having the R^1 and R^2 substituents), and E is -C(O)-N(R^5)- (where the nitrogen is bonded at the 2-position of the pyridinyl (if A is =N-) or to the phenyl (if A is =CH-) having the R^4 substituent) and R^3 is a radical of the formula (i):



(i)

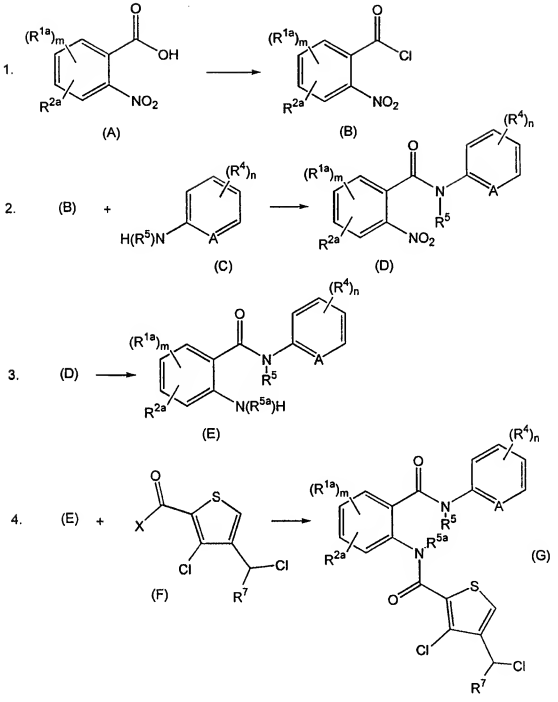
where each R^{13} and each R^{14} are as described in each following Reaction Scheme. It is understood that the other compounds of the invention may be prepared by similar methods as described herein.

A. Preparation of Compounds of Formula (Ia)

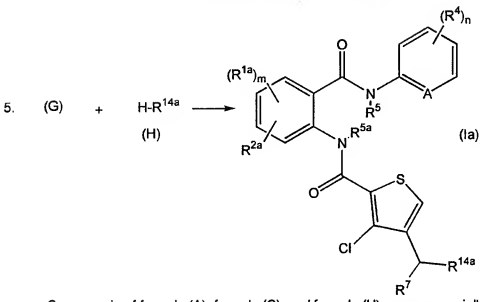
Compounds of formula (Ia) are compounds of the invention wherein R^{13} is chloro and the R^{14} substituent is in the 4-position of the thienyl radical. These compounds are prepared as described below in Reaction Scheme 1 where A is =CH- or =N-, each R^{1a} is independently hydrogen, alkyl, aryl, aralkyl, halo, cyano, -OR^5, -$S(O)_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -O-C(O)-R^5, -C(O)N(R^5)R^6, -N(R^5)R^6; R^{2a} is hydrogen, alkyl, aryl, aralkyl, halo, cyano, -OR^5, -$S(O)_p$-R^9 (where p is 0 to 2), -C(O)OR^5, -C(O)N(R^5)R^8, -N(R^{10})R^{11}, -C(R^7)H-N(R^{10})R^{11}, -C(R^7)H-R^8-N(R^{10})R^{11}, -C(R^7)H-OR^5, -C(R^7)H-R^8-OR^5, -C(R^7)H-$S(O)_p$-R^9 (where p is 0 to 2), -C(R^7)H-R^8-$S(O)_p$-R^9 (where p is 0 to 2), -O-R^8-$S(O)_p$-R^9 (where p is 0 to 2), -C(R^7)H-N(R^5)R^6, -C(R^7)H-R^8-N(R^5)R^6, -O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}, -O-R^8-N(R^{10})R^{11}, -O-R^8-O-C(O)R^5,

$-O-R^8-CH(OH)-CH_2-OR^5$, $-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-(R^8-O)_t-R^{19}$ (where t is 1 to 6), $-O-R^8-C(O)R^5$, $-O-R^8-C(O)R^{19}$, $-O-R^8-C(O)OR^5$, $-N(R^5)-R^8-N(R^{10})R^{11}$, $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2), or $-S(O)_p-R^8-C(O)OR^5$ (where p is 0 to 2); each R^4 is independently hydrogen, alkyl, halo, cyano, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, or $-R^8-N(R^5)R^6$; each R^5 and R^6 is as described above in the Summary of the Invention for compounds of formula (I); R^{5a} is hydrogen; R^7 is hydrogen or alkyl; each R^8 and R^9 are as described above in the Summary of the Invention for compounds of formula (I); each R^{10} and R^{11} is independently hydrogen, alkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{18})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$); or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, and $-C(O)N(R^5)R^6$); R^{14a} is cyano, $-N(R^{16})R^{11}$, $-N^{\oplus}(R^9)(R^{16})_2$, $-N(R^5)-R^8-C(O)OR^5$, $-S-R^{15}$, $-S-R^8-C(O)OR^5$, $-S-R^8-N(R^5)R^6$, $-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6), $-S-R^8-OR^{15}$; or R^{14a} is heterocyclyl wherein the heterocyclic ring is optionally substituted by alkyl, aryl, aralkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$; where each R^{15} and R^{16} are as described above in the Summary of the Invention for compounds of formula (I) except that neither can be or contain haloalkyl; R^{17} is as described in the Summary of the Invention for compounds of formula (I); and X is chloro or bromo:

Reaction Scheme 1



Reaction Scheme 1 continued



Compounds of formula (A), formula (C), and formula (H) are commercially available, for example, from Aldrich Co. Compounds of formula (F) are commercially available or may be prepared according to methods described herein.

In general, compounds of formula (Ia) are prepared by first reacting a compound of formula (A) in an aprotic solvent, for example, methylene chloride, at temperatures of between about -10°C to about 10°C, preferably at 0°C, with a halogenating agent, for example, oxalyl chloride. The reaction mixture is allowed to warm to ambient temperature and stirred for about 8 to 20 hours, preferably for about 16 hours, to produce a compound of formula (B), which is isolated from the reaction mixture by standard techniques (such as removal of solvents).

The compound of formula (B) in an aprotic solvent, for example, methylene chloride, at temperatures of between about -10°C to about 10°C, preferably at 0°C, is then treated with a compound of formula (C) in the presence of a base, for example, triethylamine. The reaction mixture is then stirred for about 20 to 30 minutes, preferably for about 20 minutes, at temperatures of between about -10°C to about 10°C, preferably at 0°C, then warmed to ambient temperature, and stirred for about 1 to about 20 hours, preferably for about 16 hours. The compound of formula (D) is then isolated from the reaction mixture by standard isolation techniques, such as evaporation of solvents, extraction and concentration.

The compound of formula (D) is then reduced by treatment with a reducing agent, such as tin(II) chloride under standard reducing conditions to produce a compound of formula (E), which is isolated from the reaction mixture by standard techniques.

The compound of formula (E) in an aprotic solvent, for example, methylene chloride, at

temperatures of between about -10°C to about 10°C, preferably at 0°C, is then treated with a compound of formula (F) in the presence of a base, for example, pyridine. The compound of formula (G) is then isolated from the reaction mixture by standard isolation techniques, such as concentration and trituration with water.

The compound of formula (G) in an aprotic solvent, such as DMF, at temperatures of between about -10°C to about 10°C, preferably at 0°C, is then treated with a compound of formula (H). The reaction mixture is stirred for about 20 minutes to an hour, preferably for about 30 minutes, and then allowed to warm to ambient temperature. After stirring for about 6 to about 20 hours, preferably for about 7 hours, the compound of formula (Ia) is isolated from the reaction mixture by standard isolation techniques, such as filtration and purification by flash chromatography.

The compound of formula (H) may be present as an acid salt, wherein the corresponding free base is formed *in situ* by the addition of a base to the reaction mixture, or is treated with a base prior to the reaction with the compounds of formula (G) to form the free base.

Any unprotected amino substituent must be protected prior to Step 4 to avoid acylation. Any carboxy substituent must also be esterified prior to Step 1. The resulting compounds may be deprotected when needed by appropriate methods known to those skilled in the art to afford compounds having an unsubstituted amino or carboxy substituent thereon.

Compounds of the invention where D is $-N(R^5)-S(O)_p-$ (where p is 2) may be prepared by methods disclosed above by reacting a compound of formula (E) with the sulfonyl chloride of the substituted thiophene or benzothiophene radical.

Compounds of the invention where E is $-N(R^5)-S(O)_p-$ (where p is 2), can be formed by reacting a substituted benzene sulfonyl chloride with a compound of formula (C) and then proceeding with Steps 3-5 above.

Compounds of formula (E) where R^{5a} is hydrogen may be reacted with an appropriate alkylating agent prior to Step 4 to produce compounds where R^{5a} is alkyl, aryl or aralkyl.

Compounds of the invention where R^{13} is $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0) may be prepared from the corresponding halo as described herein. Compounds where R^{13} is heterocyclylalkyl may be made from substitution from the corresponding haloalkyl.

Compounds of formula (G) may be reacted with tertiary amines of the formula $N(R^9)(R^{16})_2$ where R^9 and R^{16} are as described above in the Summary of the Invention for compounds of formula (I) by methods similar to those described above to prepare compounds of the invention wherein R^{14a} is $-N^{\oplus}(R^9)(R^{16})_2$.

Any unoxidized sulfur and nitrogen may be oxidized after the final step in Reaction

Scheme 1 by methods known to those skilled in the art to produce the desired oxidized substituents.

Compounds of formula (Ia) where R^{14a} contains a -N(H)R^{10} group may be reacted with a heterocyclic compound having a reactive halogen to form compounds where R^{14a} contains a -N(R^{10})R^{11} group wherein R^{11} is heterocyclyl.

Compounds of formula (Ia) where R^{14a} contains a secondary amino substituent may be reacted with an aldehyde in an aprotic solvent, such as acetonitrile, in the presence of a reducing agent such as sodium cyanoborohydride to form compounds wherein the amino substituent is further substituted by an alkyl or aralkyl group.

Compounds of formula (Ia) where R^{14a} is -N(R^{10})R^{11} where R^{10} is hydrogen and R^{11} is -R^{8}-OR^{5} (where R^{5} is hydrogen and R^{8} is ethyl or propyl optionally substituted by alkyl or alkoxyalkyl) can be reacted with cyanogen bromide to form compounds of the invention where R^{14} is -C(R^{7})H-N(R^{10})R^{11} where R^{10} and R^{11} together with the nitrogen to which they are attached form optionally substituted 2-iminooxazolidin-3-yl or optionally substituted tetrahydro-2-amino-1,3-oxazinyl.

Compounds of formula (Ia) where R^{14a} is -N(R^{10})R^{11} where R^{11} is hydrogen and R^{10} is alkyl, aryl or aralkyl can be reacted with a cyano halide under basic conditions to form compounds of the invention where R^{14} is -C(R^{7})H-N(R^{10})-CN, which can then be reacted with an azide in the presence of tributyl tin chloride in an aprotic solvent to form a compound of the invention where R^{14} is -C(R^{7})H-N(R^{10})R^{11} where R^{11} is tetrazolyl attached to the nitrogen through a carbon atom in the heterocyclic ring.

Compounds of formula (G) may be treated with an oxidizing agent to form the corresponding *N*-oxide when A is =N-, and then treated with compounds of formula (H) to form other compounds of the invention where the pyridinyl ring is oxidized.

Compounds of formula (Ia) where R^{14a} is -N(R^{10})R^{11} where R^{10} is hydrogen and R^{11} is -R^{8}-N(R^{5})R^{6} where R^{8} is ethyl or propyl and at least one R^{5} or R^{6} is hydrogen may be further treated with an ortho ester under mild acidic conditions to form compounds of the invention where R^{14} is -C(R^{7})H-N(R^{10})R^{11} where R^{10} and R^{11} together with the nitrogen form an optionally substituted imidazolinyl. Other compounds of the invention may be similarly made. Such compounds wherein the imidazolinyl is substituted with an appropriate haloalkyl may be further treated with a compound of formula (H) in an aprotic solvent to form compounds wherein the imidazolinyl is substituted by the corresponding R^{14a} group.

Compounds of formula (Ia) where R^{14a} is -N(R^{10})R^{11} where R^{10} and R^{11} together with the nitrogen form a 2-aminoimidazolyl in a protic solvent of the formula R^{5}-OH may be further treated with a halogenating agent, such as *N*-chlorosuccinimide (NCS) in the presence of a strong acid to

form compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^{10} and R^{11} form a 2-iminoimidazolidinyl substituted at the 4- and 5-position with $-OR^5$. Other compounds of the invention may be similarly made.

Compounds of formula (Ia) where R^{14a} is $-N(R^{10})R^{11}$ where R^{10} is hydrogen and R^{11} is $-R^8-N(R^5)R^6$ where either R^5 or R^6 is hydrogen may be further treated with phosphoryl chloride in the presence of a base, followed by treatment with a compound of the formula R^5-OH to form compounds of the invention where R^{14} is $-C(R^7)H-N(R^5)-P(O)(OR^5)_2$.

Compounds of formula (Ia) where R^{14a} is $-N(R^{10})R^{11}$ where R^{10} and R^{11} together with the nitrogen form 2-methylthioimidazolinyl may be further treated with $N(R^5)H-R^8-OR^5$ or with $NH_2-R^8-C(O)-N(R^5)R^6$ to form compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^{10} and R^{11} together with the nitrogen form a imidazolinyl substituted at the 2-position with $-N(R^5)-R^8-OR^5$ or with $=NR^{17}$ where R^{17} is $-R^8-C(O)-N(R^5)R^6$, respectively.

Compounds of formula (Ia) where R^{14a} is $-N(R^{10})R^{11}$ where R^{10} and R^{11} together with the nitrogen form a *N*-heterocyclic substituted with formyl may be treated under standard reducing conditions to form compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^{10} and R^{11} together with the nitrogen form a *N*-heterocyclic substituted with hydroxymethyl. Other compounds of the invention may be similarly made.

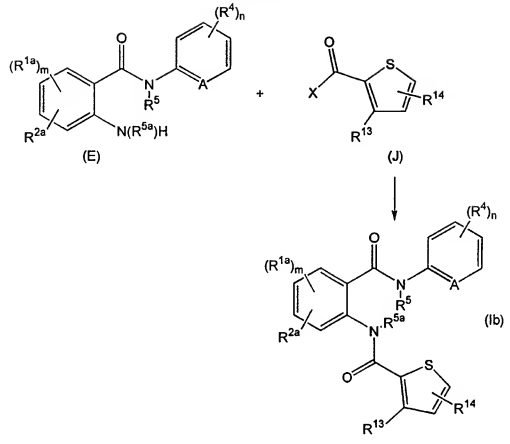
Compounds of formula (Ia) where R^{14a} is $-N(R^{10})R^{11}$ where R^{10} is alkyl and R^{11} is oxazolin-2-yl may be treated with compounds of the formula R^5-C(O)OH to form compounds of the invention where R^{14} is $-N(R^{10})R^{11}$ where R^{10} is alkyl and R^{11} is $-C(O)-N(R^5)R^{15}$ where R^5 is hydrogen and R^{15} is $-R^8-O-C(O)R^5$ where R^8 is ethyl.

Other compounds of formula (Ia) may be prepared according to the methods described herein according to methods known to those skilled in the art.

B. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) are compounds of the invention and are prepared as follows in Reaction Scheme 2 wherein A is =CH- or =N-, each R^{1a} is as defined in Reaction Scheme 1 above; R^{2a} is as defined in Reaction Scheme 1 above; R^5 is as defined in the Summary of the Invention for compounds of formula (I); R^{5a} is hydrogen; each R^4 and R^{13} is as defined in the Summary of the Invention for compounds of formula (I), R^{14} is as described above in the Summary of the Invention for compounds of formula (I); and X is chloro or bromo:

Reaction Scheme 2



Compounds of formula (E) are prepared above in Reaction Scheme 1. Compounds of formula (J) are commercially available, *e.g.*, from Lancaster, or may be prepared by methods known to those skilled in the art from compounds of formula (J) where X is $-OCH_3$ (and where R^{13} or R^{14} do not contain a hydrolyzable group such as an ester), which is hydrolyzed to the acid and then converted to the acid chloride to form a compound of formula (J). In addition, compounds of formula (J) may be prepared according to methods disclosed herein.

In general, compounds of formula (Ib) are prepared by treating a compound of formula (E) with a compound of formula (J) in the presence of a base, preferably pyridine, at temperatures of between about -10°C to about 10°C, preferably at 0°C. The reaction mixture is allowed to warm to ambient temperature and then stirred for about 8 to 20 hours, preferably for about 16 hours. The compound of formula (Ib) is then isolated from the reaction mixture by standard isolation techniques, such as filtration and recrystallization.

Compounds of formula (Ib) where R^{14} is hydrogen, halo, formyl, acetyl, $-N(R^{10})R^{11}$, $-N(R^5)-R^8-C(O)OR^5$, $-C(O)OR^5$, $-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-S(O)_p-N(R^5)R^6$, or

-C(O)N(R^5)R^6; and R^{1a}, R^{2a} or R^{13} is alkyl, may be treated under standard halogenating conditions to form compounds where R^{1a}, R^{2a} or R^{13} is haloalkyl. The resulting compounds may then be treated with HN(R^{10})R^{11} or HN(R^5)R^6 to form compounds where R^{1a}, R^{2a} or R^{13} is -C(R^7)H-N(R^{10})R^{11} or -C(R^7)H-N(R^5)R^6.

Compounds of formula (Ib) where R^{14} is cyano may be treated with methanol or ethanol to form the corresponding imidate, which can then be treated with a compound of formula NH_2-R^8-N(R^5)R^6 where at least one R^5 or R^6 is hydrogen to form compounds of the invention where R^{14} is heterocyclyl containing at least two nitrogen atoms. Altematively, the imidate so formed can be treated with a compound of formula N(H)(R^5)R^6 to form compounds of the invention where R^{14} is -C(NH)-N(R^5)R^6 which can be further treated under conditions similar to those described herein to form compounds of the invention where R^{14} is -C(NR^{17})-N(R^5)R^6 where R^{17} is as described above in the Summary of the Invention for compounds of formula (I).

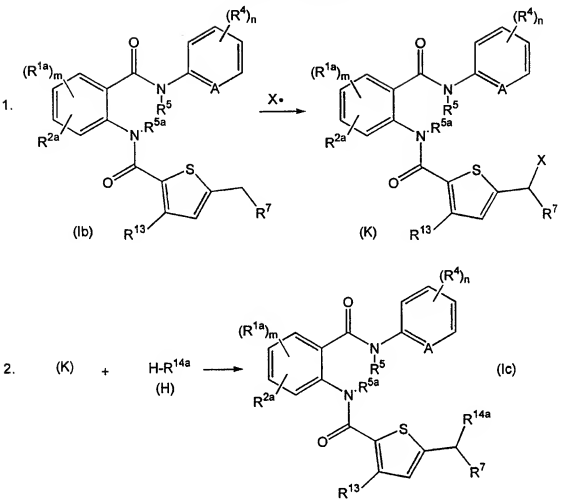
Compounds of formula (Ib) where one or more R^{1a}s is hydroxy and R^2 is hydrogen may be further treated with a compound of formula R^5-C(O)-X where X is chloro or bromo to produce compounds of the invention where one or more R^{1a}s is -O-C(O)-R^5.

Compounds of formula (Ib) where R^{14} is -N(R^{10})R^{11} where at least one R^{10} or R^{11} is hydrogen can be treated with the appropriate X-C(O)-R^{15} where X is bromo or chloro and R^{15} is as described above in the Summary of the Invention for compounds of formula (I) to form compounds of the invention where R^{14} is -N(R^{10})(R^{11}) where R^{10} is hydrogen, alkyl, aryl or aralkyl and R^{11} is -C(O)-R^{15}. During this process, other substitutents of compounds of formula (Ib) which contain a reactive hydroxy, amino or carboxy group may also be acylated.

C. Preparation of Compounds of Formula (Ic)

Compounds of formula (Ic) are compounds of the invention. They are prepared from compounds of formula (Ib) where A is =CH- or =N-, R^{14b} is -CH_2-R^7 where R^7 is hydrogen or alkyl as illustrated below in Reaction Scheme 3 wherein each R^{1a}, R^{2a}, R^4, R^5, R^{5a} and R^{14a} are as defined above in Reaction Scheme 1, and R^{13} is as defined above in the Summary of the Invention for compounds of formula (I), and X is bromo and chloro:

Reaction Scheme 3



Compounds of formula (Ib) are prepared herein. Compounds of formula (H) are commercially available or may be prepared according to methods known to those skilled in the art or by methods disclosed herein.

In general, compounds of formula (Ic) are prepared by first treating a compound of formula (Ib) in an organic solvent, such as benzene, with an halogenating agent under conditions to form the halide radical (such as irradiation). The compound of formula (K) is then isolated from the reaction mixture by standard techniques, such as concentration and trituration with solvent.

The compound of formula (K) in an aprotic solvent, such as methylene chloride, is treated with a compound of formula (H). The reaction mixture is stirred at ambient temperature for about 8 to about 20 hours, preferably for about 18 hours. The compound of formula (Ic) is then isolated from the reaction mixture by standard isolation techniques, such as extraction, concentration and

purification by HPLC.

Compounds of the invention where R^{13} is haloalkyl may be prepared by halogenating the corresponding alkyl substituent according to methods known to those skilled in the art. The compounds so formed can then be treated with the appropriate $HN(R^5)R^6$ group under conditions similar to those described above for preparing compounds of formula (Ic) to produce compounds of the invention where R^{13} is $-C(R^7)H-N(R^5)R^6$.

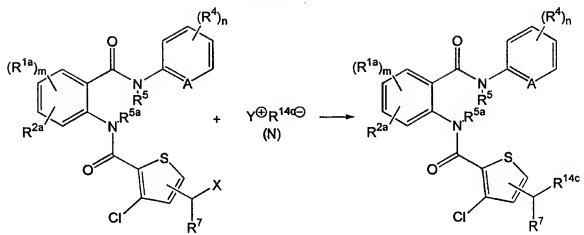
For better yield in the above Reaction Scheme, it is recommended that R^{1a}, R^{2a}, R^4, and R^{13} do not contain an alkyl group, since this alkyl will also be halogenated and will subsequently react with compound of formula (H) during the reaction.

Compounds of formula (K) where X is bromo may be treated under standard substitution conditions to form compounds of formula (Ic) where R^{14a} is hydroxy. These compounds may be further oxidized under standard oxidizing conditions to form compounds of the invention where R^{14} is formyl, which can further oxidized to form compounds of the invention where R^{14} is $-C(O)OR^5$.

D. Preparation of Compounds of Formula (Id)

Compounds of formula (Id) are compounds of the invention where R^{13} is chloro. They are prepared from compounds of formula (M) which are compounds of either formula (G) or (K) as illustrated below in Reaction Scheme 4 where A is =CH- or =N-, each R^{1a}, R^{2a}, each R^4, R^5, R^{5a} and R^7 are as defined above in Reaction Scheme 1; R^{14c} is $-OR^5$, $-S-R^{15}$, $-S-R^8-C(O)OR^5$, $-S-R^8-N(R^5)R^6$, $-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S-R^8-OR^5$, -CN or $-N(R^{10})R^{11}$ (where R^{10} and R^{11} together with the nitrogen to which they are attached form a a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocylic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17a})$, $-OR^{5b}$, $-C(O)OR^{5b}$, $-R^8-C(O)OR^{5b}$, $-N(R^{5b})R^{6b}$, $-R^8-N(R^{5b})R^{6b}$, $-C(O)N(R^{5b})R^{8b}$, $-R^8-C(O)N(R^{5b})R^{8b}$, $-N(R^{5b})-N(R^{5b})R^{6b}$, $-C(O)R^{5b}$, $-C(O)-(R^8-O)_t-R^{5b}$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^{5b}$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^{5b}$, $-C(O)OR^{5b}$, $-N(R^5)R^{6b}$, and $-C(O)N(R^{5b})R^{6b}$) where R^{5b} and R^{6b} are alkyl, aryl or aralkyl and R^{17a} is as defined for R^{17} in the Summary of the Invention for compounds of formula (I) except R^{17a} can not be hydrogen; and where each R^8, R^9 and R^{15} are as defined above in the Summary of the Invention for compounds of formula (I); and Y is a metal cation:

Reaction Scheme 4



Compounds of formula (N) are commercially available or may be prepared according to methods known to those skilled in the art.

In general, the compounds of formula (Id) are prepared by reacting a compound of formula (M) in an aprotic solvent with a compound of formula (N). The reaction mixture is stirred at ambient temperature for about 8 to about 20 hours, preferably for about 16 hours. The compound of formula (Id) is then isolated from the reaction mixture by standard isolation techniques, such as extraction, concentration of product, and flash chromatography.

Alternatively, a compound of formula HR^{14c} in an aprotic solvent, such as DMF, is treated with a strong base, such as sodium hydride, at ambient temperature to form the corresponding salt. The compound of formula (M) in an aprotic solvent, such as DMF, is then added to the reaction mixture containing the salt. The reaction mixture is stirred at ambient temperature for about 10 to 20 hours, preferably for about 18 hours. The compound of formula (Id) is then isolated from the reaction mixture by standard isolation techniques, such as extraction, concentration and flash chromatography.

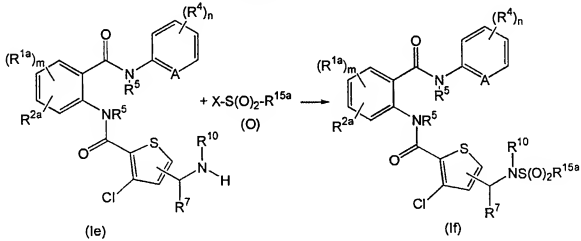
In general, this reaction scheme is used for those amines, alcohols and mercapto compounds of formula HR^{14c} which are not reactive enough to be used in Reaction Schemes 1 or 2 above. The salt can be formed *in situ* or can be isolated.

Compounds of formula (Ia) where R^{14c} is cyano may be further treated with hydroxylamine under basic conditions in a protic solvent to form compounds of the invention where R^{14} is $-C(R^7)H-C(NR^{17})-R^{10}$ where R^{17} is -OH.

E. Preparation of Compounds of Formula (If)

Compounds of formula (If) are compounds of the invention wherein a R^{14} substituent is $-C(R^7)H-N(R^{10})R^{11}$ where R^7 is hydrogen or alkyl, R^{10} is hydrogen, alkyl, aryl, aralkyl, $-OR^5$ (where R^5 is not hydrogen), $-R^8-OR^5$ (where R^5 is not hydrogen), $-R^8-N(R^5)R^6$, cycloalkyl (optionally substituted as described above in the Summary of the Invention for compounds of formula (I) except that R^5 can not be hydrogen), and heterocyclylalkyl (optionally substituted as described above in the Summary of the Invention for compounds of formula (I) except that R^5 can not be hydrogen) , and R^{11} is $-S(O)_2-R^{15a}$ where R^{15a} is alkyl, haloalkyl, aryl, aralkyl, $-R^8-O-C(O)-R^5$, $-R^8-OR^5$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^{5b}$, $-R^8-OR^{5b}$, $-C(O)OR^{5b}$, $-N(R^{5b})R^{6b}$ and $-C(O)N(R^{5b})R^{6b}$ where each R^{5b} and R^{6b} is alkyl, aryl or aralkyl), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^{5b}$, $-R^8-OR^{5b}$, $-C(O)OR^{5b}$, $-N(R^{5b})R^{6b}$ or $-C(O)N(R^{5b})R^{6b}$ where each R^{5b} or R^{6b} is alkyl, aryl or aralkyl). They are prepared from compounds of formula (M) as illustrated below in Reaction Scheme 5 where A is =CH- or =N-; R^{1a}, R^{2a}, R^4, R^5 and R^{5a} are as described above in Reaction Scheme 1; R^{10} and R^{15a} are as described above; and X is chloro or bromo:

Reaction Scheme 5



Compounds of formula (O) are commercially available or may be prepared according to methods known to those of ordinary skill in the art. The compound of formula (Ie) is a compound of formula (Ia) where R^{14a} is $-N(R^{10})R^{11}$ and is prepared herein.

In general, compounds of formula (If) are prepared by treating a compound of formula (Ie)

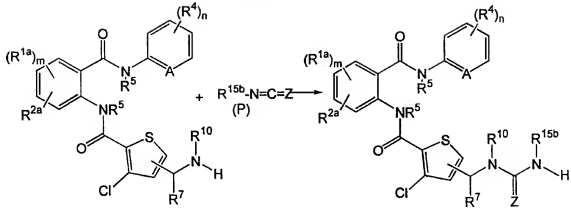
in the presence of base, such as pyridine, at temperatures of between about -10°C to about 10°C, preferably at 0°C, with a compound of formula (O). The reaction mixture is allowed to warm to ambient temperature and then stirred for about 8 to about 20 hours, preferably for about 16 hours. The compound of formula (If) is then isolated from the reaction mixture by standard isolation techniques, such as removal of solvents *in vacuo* and purification by flash chromatography.

This reaction scheme can also be used with compounds of the formula $X\text{-}S(O)_2\text{-}N(R^{10})R^{11}$ to make compounds of the invention where R^{14} is $-C(R^7)H\text{-}N(R^{10})\text{-}S(O)_2\text{-}N(R^{10})R^{11}$.

F. Preparation of Compounds of Formula (Ig)

Compounds of formula (Ig) are compounds of the invention wherein a R^{14} is $-C(R^7)H\text{-}N(R^{10})R^{11}$ where R^7 is hydrogen or alkyl, R^{10} is hydrogen, alkyl, aryl, aralkyl, $-OR^5$ (where R^5 is not hydrogen), $-R^8\text{-}OR^5$, $-R^8\text{-}N(R^5)R^6$, cycloalkyl (optionally substituted as described above in the Summary of the Invention for compounds of formula (I) except that R^5 can not be hydrogen), and heterocyclylalkyl (optionally substituted as described above in the Summary of the Invention for compounds of formula (I) except that R^5 can not be hydrogen); and R^{11} is either $-C(O)\text{-}N(R^5)R^{15b}$ or $-C(S)\text{-}N(R^5)R^{15b}$ where each R^5 is hydrogen and each R^{15b} is hydrogen, alkyl, aryl, aralkyl, $-R^8\text{-}OR^5$, $-R^8\text{-}C(O)OR^5$ or heterocyclylalkyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^5$). They are prepared as described below in Reaction Scheme 6 wherein A is =CH- or =N-; R^{1a}, R^{2a}, R^4, R^5, and R^{5a} are as described above in Reaction Scheme 1; and R^{15b} is as described above; and Z is either oxygen or sulfur:

Reaction Scheme 6



Compounds of formula (P) are commercially available, or may be prepared according to methods known to those skilled in the art. The compounds of formula (Ie) are compounds of formula (Ia) where R^{14a} is $-N(R^{10})R^{11}$ and are prepared by methods disclosed herein.

In general, compounds of formula (Ig) are prepared by treating a compound of formula (Ie) in an aprotic solvent, such as dioxane, with a compound of formula (P). The reaction mixture is stirred at ambient temperature for about 8 to about 20 hours, preferably for about 16 hours. The compound of formula (Ig) is isolated from the reaction mixture by standard isolation techniques, such as concentration of product and purification by flash chromatography.

Alternatively, to produce compounds of formula (Ig) where R^{15b} is hydrogen, compounds of formula (Ie) may be reacted with potassium isocyanate (K-N=C=O). Alternatively, compounds of formula (Ie) may be reacted first with phosgene or equivalent, followed by reacting the resulting product with a disubstituted amine or a cyclic amine to form compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^{10} is as described above for the compounds of formula (Ig) and R^{11} is $-C(O)-N(R^5)R^{15}$ where R^5 and R^{15} are independently alkyl, aryl or aralkyl, or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring as defined in the Summary of the Invention for compounds of formula (I).

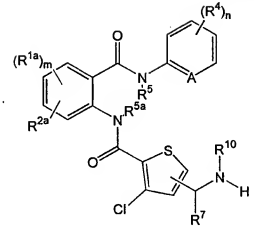
Compounds of formula (Ig) where R^{15b} is hydrogen can be further reacted with a halocetaldehyde dialkylacetal in the presence of a protic solvent, preferably an alkanol, to form compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^7 is hydrogen or alkyl, and R^{10} is as described above for the Reaction Scheme and R^{11} is an oxazol-2-yl substituent.

G. Preparation of Compounds of Formula (Ih) and (Ij)

Compounds of formula (Ih) and (Ij) are compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^7 is hydrogen or alkyl, R^{10} is hydrogen, alkyl, aryl or aralkyl, and R^{11} is $-C(O)-R^{15}$ where R^{15} is $-R^8-OR^5$, $-R^8-N(R^5)R^6$ or heterocyclylalkyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$ (where R^5 and R^6 are as described above in the Summary of the Invention for compounds of formula (I))). These compounds are prepared as described below where A is =CH- or =N-; R^{1a}, R^{2a}, R^4, R^5, R^{5a} are as described above in Reaction Scheme 1; and R^7 and R^8 are as described in the Summary of the Invention for compounds of formula (I); and R^{15c} is $-OR^5$, $-N(R^5)R^6$ or heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^5$ (where R^5 and R^6 are as described above in the Summary of the Invention for compounds of formula (I))), for example, 4-methylpiperidine; and each X is independently bromo or chloro:

Reaction Scheme 7

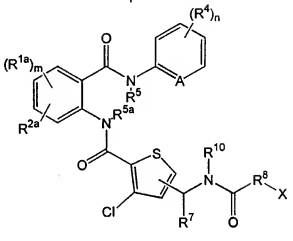
1.



(Ie)

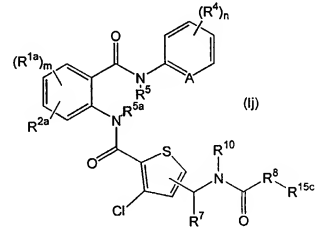
+

(Q)



(Ih)

2. (Ih) + H-R^{15c} (R)



(Ij)

Compounds of formula (Q) and formula (R) are commercially available or may be prepared by methods known to those skilled in the art.

In general, the compounds of formula (Ij) are prepared by first treating a compound of

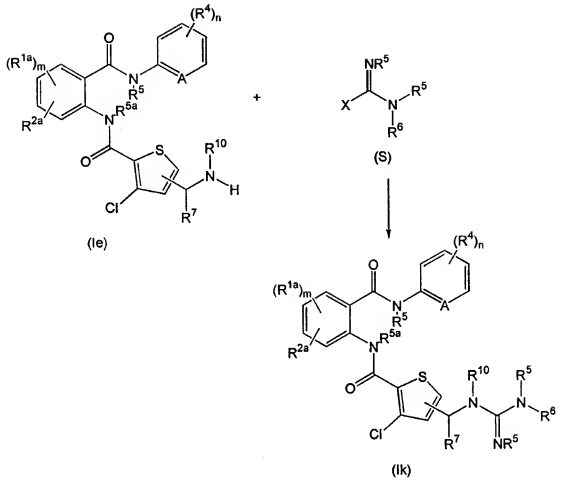
formula (Ie) in an aprotic solvent, such as methylene chloride, in the presence of a base, such as diisopropylethylamine, at temperatures of between about -10°C and about 10°C, preferably at about 0°C, with a compound of formula (Q). The reaction mixture was allowed to warm to ambient temperature and stirred for about 4 to about 10 hours, preferably for about 7 hours. A compound of formula (R) is then added to the reaction mixture and the resulting reaction mixture is stirred about 10 to about 20 hours, preferably for about 16 hours. The compound of formula (Ij) is isolated from the reaction mixture by standard isolation techniques, such as concentration and purification by HPLC.

Alternatively, the compound of formula (Q) could be phosgene (Cl-C(O)-Cl). Under these circumstances, the final product would have the R^{15c} substituent directly attached to the carbonyl in the compound of formula (Ij). Alternatively, the compound of formula (Q) could also be $X\text{-}S(O)_z\text{-}R^8\text{-}X$ to produce compounds of the invention where R^{14} is $-C(R^7)H\text{-}N(R^{10})R^{11}$ where R^{10} is as described above for compounds of formula (Ij) and R^{11} is $-S(O)_z\text{-}R^{15}$ where R^{15} is as described above for R^{15}.

H. Preparation of Compounds of Formula (Ik)

Compounds of formula (Ik) are compounds of the invention where R^{14} is $-C(R^7)H\text{-}N(R^{10})\text{-}C(NR^{17})\text{-}N(R^5)R^6$ where each R^5 is as described in the Summary of the Invention for compounds of formula (I), where R^6 and R^7 are as described in the Summary of the Invention for compounds of formula (I), R^{10} is hydrogen, alkyl, aryl or aralkyl, and R^{17} is hydrogen, alkyl, aryl or aralkyl. They are prepared as illustrated below in Reaction Scheme 8 where A is =CH- or =N-; R^{1a}, R^{2a}, R^4, R^5 and R^{5a} are as described above in Reaction Scheme 1; R^6 and R^7 are as described in the Summary of the Invention for compounds of formula (I); R^{10} is hydrogen, alkyl, aryl or aralkyl; R^{17} is hydrogen, alkyl, aryl or aralkyl; and X is bromo or chloro, or X can also be other leaving groups such as alkylthio (methylthio) or pyrazolyl:

Reaction Scheme 8



Compounds of formula (S) are commercially available, or may be prepared according to methods known to those skilled in the art.

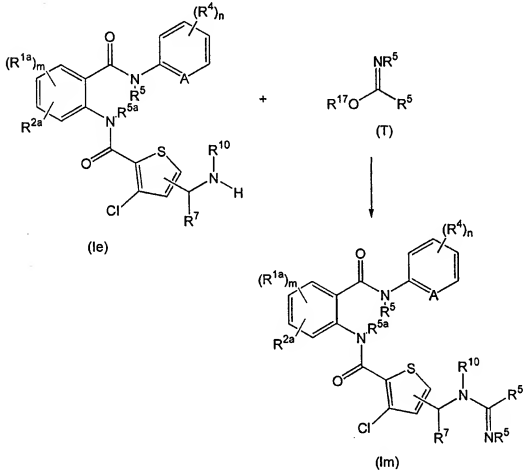
In general, compounds of formula (Ik) are prepared by treating a compound of formula (Ie) in an aprotic solvent, such as DMF, in the presence of a base, such as triethylamine, with a compound of formula (S). The reaction mixture is stirred at ambient temperature to about 50°C, preferably at about 45°C, for about 2 to about 4 hours, preferably for about 3 hours. The reaction mixture is allowed to cool to ambient temperature and acidified, preferably with trifluoroacetic acid. The compound of formula (Ik) is isolated from the reaction mixture by standard isolation techniques, such as purification by HPLC.

I. Preparation of Compounds of Formula (Im)

Compounds of formula (Im) are compounds of the invention where R^{14} is

-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10} where R^7 is as described in the Summary of the Invention for compounds of formula (I) and each R^{10} and R^{17} are independently hydrogen, alkyl, aryl or aralkyl. They are prepared as illustrated below in Reaction Scheme 9 where A is =CH- or =N-; R^{1a}, R^{2a}, R^4, each R^5 and R^{5a} are as described above in Reaction Scheme 1; R^7 is as described in the Summary of the Invention for compounds of formula (I); R^{10} and R^{17} are each independently hydrogen, alkyl, aryl or aralkyl; and R^{20} is alkyl:

Reaction Scheme 9



Compounds of formula (T) are commercially available or may be prepared according to methods known to those skilled in the art, or by methods described herein. Compounds of formula (Ie) are prepared herein.

In general, compounds of formula (Im) are prepared by treating a compound of formula (Ie) in a protic solvent, such as methanol, with a compound of formula (T). The reaction mixture is stirred at ambient temperature for about 8 to about 20 hours, preferably for about 16

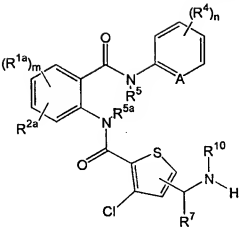
hours. The compound of formula (Im) is then isolated from the reaction mixture by standard isolation techniques, such as concentration and purification by HPLC.

J. Preparation of Compounds of Formula (In) and (Io)

Compounds of formula (In) are compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^7 is hydrogen or alkyl, R^{10} is hydrogen, alkyl, aryl or aralkyl and R^{11} is $-C(O)-N(R^5)R^{15}$ or $-C(S)-N(R^5)R^{15}$; and compounds of formula (Io) are compounds of the invention where R^{14} is $-C(R^7)H-N(R^{10})R^{11}$ where R^7 is hydrogen or alkyl and R^{10} is hydrogen, alkyl, aryl or aralkyl, and R^{11} is heterocyclyl (optionally substituted by alkyl or oxo). They are prepared as illustrated below where A is =CH- or =N-; R^{1a}, R^{2a}, R^4, each R^5 and R^{5a} are as described above in Reaction Scheme 1; R^7 is as described in the Summary of the Invention for compounds of formula (I); R^{10} is hydrogen, alkyl, aryl or aralkyl; Z is oxygen or sulfur; n is 2 or 3; and X is bromo or chloro:

Reaction Scheme 10

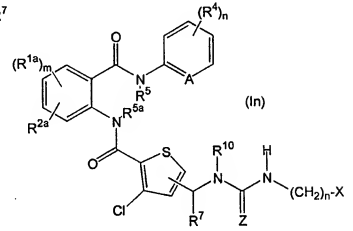
1.



+ X-(CH$_2$)$_n$-N=C=Z

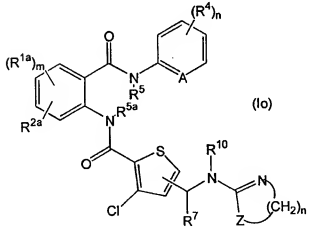
(U)

(Ie)



(In)

2. (In) ⟶



(Io)

Compounds of formula (U) are commercially available or may be prepared according to methods known to those skilled in the art. Compounds of formula (Ie) are prepared herein.

In general, compounds of formula (Io) are prepared by first treating a compound of formula (Ie) in an aprotic solvent, such as tetrahydrofuran, at temperatures of about -10°C to

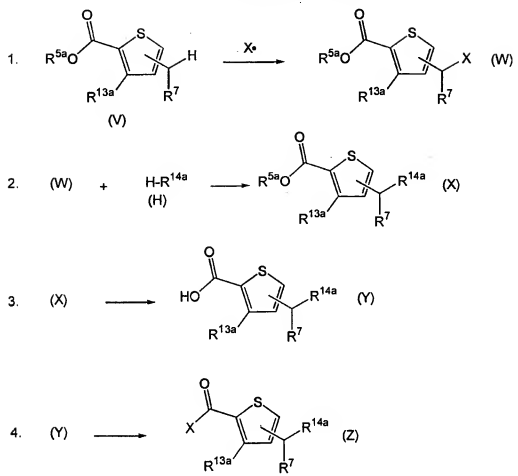
about 10°C, preferably at about 0°C, with an excess molar amount of a compound of formula (U). The reaction mixture is stirred at ambient temperature for about 4 to 10 hours, preferably for about 7 hours to form a compound of formula (In). The reaction mixture is cooled to a temperature of about -10°C to about 10°C, preferably to about 0°C, and a mild base, preferably triethylamine, is added to the reaction mixture. The resulting reaction mixture is then warmed to ambient temperature and stirred for about 20 to 30 hours, preferably for about 24 hours. The compound of formula (Io) is then isolated from the reaction mixture by standard isolation techniques, such as concentration of volatiles and purification by flash chromatography.

Other compounds of formula (U) may be used to produce compounds of formula (Io) wherein the heterocyclyl ring so formed is substituted by alkyl or by oxo. For example, if the nitrogen of the isocyanate is substituted by a branched alkyl with the terminal halo atom being 2 to 3 carbons away from the nitrogen, the compound so formed would have an alkyl substituent off the heterocyclic ring in the compound of formula (Io). Also, if the nitrogen is substituted by $-C(O)-R^{17}$ where R^{17} is a haloalkyl (where the halo is on the terminal carbon of the haloalkyl group), one would end up with a heterocyclic ring with an oxo substituent next to the nitrogen atom of the heterocyclic.

K. Preparation of Compounds of Formula (Z)

Compounds of formula (Z) are intermediates in the preparation of the compounds of the invention and are prepared as illustrated below where R^{5a} is alkyl, R^7 is hydrogen or alkyl, R^{13a} is hydrogen, halo, $-OR^5$ (where R^5 is alkyl, aryl or aralkyl); and R^{14a} is as described above in Reaction Scheme 1; and each X is bromo or chloro:

Reaction Scheme 11



Compounds of formula (V) and formula (H) are commercially available or may be prepared according to methods known to those skilled in the art or methods disclosed herein.

In general, compounds of formula (Z) are prepared by first reacting a compound of formula (V) in an aprotic solvent, such as carbon tetrachloride, with a halogenating agent, such as sulfuryl chloride, in the presence of a catalytic agent, such as benzoyl peroxide. The reaction mixture is heated at reflux for about 12 to about 20 hours, preferably for about 17 hours, then cooled to ambient temperature. The compound of formula (W) is then isolated from the reaction mixture by standard isolation techniques, such as concentration of volatiles and purification by flash chromatography.

The compound of formula (W) in an aprotic solvent, such as methylene chloride, is then treated with a compound of formula (H). The resulting reaction mixture is then stirred at ambient temperature for about 10 to about 20 hours, preferably for about 16 hours. The compound of

formula (X) is then isolated from the reaction mixture by standard isolation techniques, such as concentration of the product and purification by flash chromatography.

The compound of formula (X) in a protic solvent, such as ethanol, is then hydrolyzed under basic hydrolysis conditions (for example, by the addition of a strong base, such as sodium hydroxide) at ambient temperature. The compound of formula (Y) is then isolated from the reaction mixture by standard isolation techniques, such as concentration of volatiles, dissolution of product in water, acidification of the aqueous solution with a strong acid and filtration.

The compound of formula (Y) is then converted to a compound of formula (Z) by standard techniques.

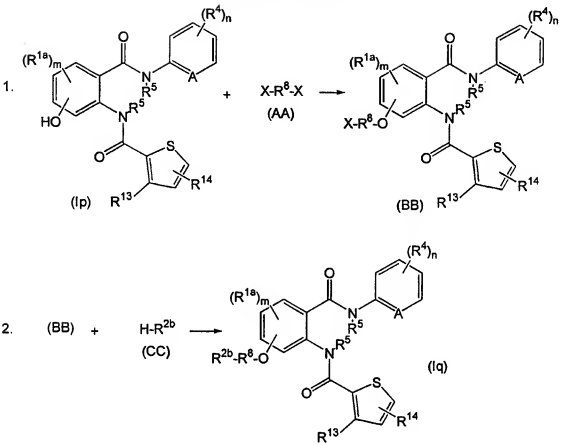
Alternatively, the compound of formula (Y) can be isolated as the metal salt and then converted as is to a compound of formula (Z) by standard techniques.

Compounds of formula (Z) may be then be reacted with compounds of formula (E) to prepare compounds of the invention as described above in Reaction Scheme 1.

L. Preparation of Compounds of Formula (Iq)

Compounds of formula (Iq) are compounds of the invention wherein R^2 is $-O-R^8-N(R^{10})R^{11}$ where R^8 is as defined in the Summary of the Invention for compounds of formula (I) and R^{10} and R^{11} are as defined in the Summary of the Invention for compounds of formula (I) except that neither can be $-OR^5$, $-S(O)_2-R^{15}$, $-C(O)-R^{15}$, $-C(O)-N(R^5)R^{15}$ or $-C(S)-N(R^5)R^{15}$. They are prepared as illustrated below in Reaction Scheme 12 where A is =CH- or =N-; R^{18}, R^4 and R^{14} are as described in the Summary of the Invention for compounds of formula (I) except that none can be hydroxy, amino, carboxy or contain a nucleophilic amine; and R^5 and R^6 are as described in the Summary of the Invention for compounds of formula (I); and R^{2b} is $-N(R^{10})R^{11}$ where R^{10} and R^{11} are as defined above; and R^{13} is as described in the Summary of the Invention for compounds of formula (I) except that R^{13} can not be haloalkyl where the alkyl is substituted by only one halogen atom or R^{13} can not contain a nucleophilic nitrogen, and each X is bromo or chloro:

Reaction Scheme 12



Compounds of formula (AA) and (CC) are commercially available. Compounds of formula (Ip) are prepared by methods disclosed herein.

In general, compounds of formula (Iq) are prepared by treating a compound of formula (Ip) in an aprotic solvent, such as DMF, in the presence of a base, such as cesium carbonate, with a compound of formula (AA). The reaction mixture is stirred at ambient temperature for about 16 to about 20 hours to make the compound of formula (BB). A compound of formula (CC) is added to the reaction mixture and the resulting reaction mixture is heated to temperatures of between about 60°C and 70°C, preferably to about 65°C. The reaction mixture is maintained at that temperature for about 10 to about 14 hours, preferably for about 12 hours. The reaction mixture is then cooled to ambient temperature and the compound of formula (Iq) is isolated from the reaction mixture by standard isolation techniques, such as filtration and purification by HPLC.

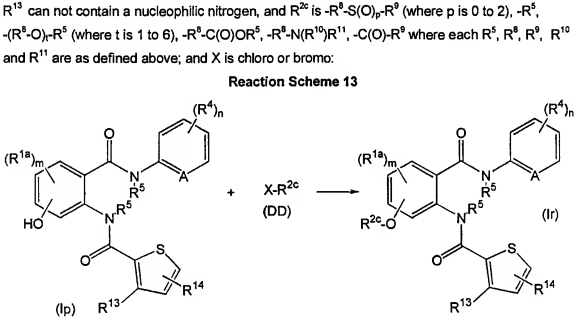
When the compound of formula (CC) is a non-reactive amine, the anion of the amine may be prepared prior to reacting with the compound of formula (BB) to form the compound of formula

(Iq). Such non-reactive amines include, but are not limited to, imidazole, tetrazole, and pyrazole.

M. Preparation of Compounds of Formula (Ir)

Compounds of formula (Ir) are compounds of the invention wherein R^2 is -O-R^8-S(O)$_p$-R^9 (where p is 0 to 2), -OR^8, -O-(R^8-O)$_t$-R^5 (where t is 1 to 6), -O-R^8-C(O)OR^5, -O-R^8-N(R^{10})R^{11}, -O-C(O)-R^5 where each R^5, R^9 and R^8 are as defined above in the Summary of the Invention for compounds of formula (I); and R^{10} and R^{11} are as defined above in the Summary of the Invention for compounds of formula (I). They are prepared as illustrated below in Reaction Scheme 13 where A is =CH- or =N-; R^{1a}, R^4 and R^{14} are as described in the Summary of the Invention for compounds of formula (I) except that none can be hydroxy, amino, carboxy or contain a nucleophilic amine; and R^5 and R^8 are as defined in the Summary of the Invention for compounds of formula (I), and R^{13} is as described in the Summary of the Invention for compounds of formula (I) except that R^{13} can not be haloalkyl where the alkyl is substituted by only one halogen atom or R^{13} can not contain a nucleophilic nitrogen, and R^{2c} is -R^8-S(O)$_p$-R^9 (where p is 0 to 2), -R^5, -(R^8-O)$_t$-R^5 (where t is 1 to 6), -R^8-C(O)OR^5, -R^8-N(R^{10})R^{11}, -C(O)-R^5 where each R^5, R^8, R^9, R^{10} and R^{11} are as defined above; and X is chloro or bromo:

Reaction Scheme 13



Compounds of formula (DD) are commercially available or may be prepared according to methods known to those of ordinary skill in the art. Compounds of formula (Ip) are prepared herein.

In general, compounds of formula (Ir) are prepared by treating a compound of formula (Ip) in an aprotic solvent, such as DMF, in the presence of a strong base, such as sodium hydride, at ambient temperature with a compound of formula (DD). The reaction mixture is stirred for about 1 hour to about 4 hours, preferably for about 3 hours, and then cooled to temperatures of

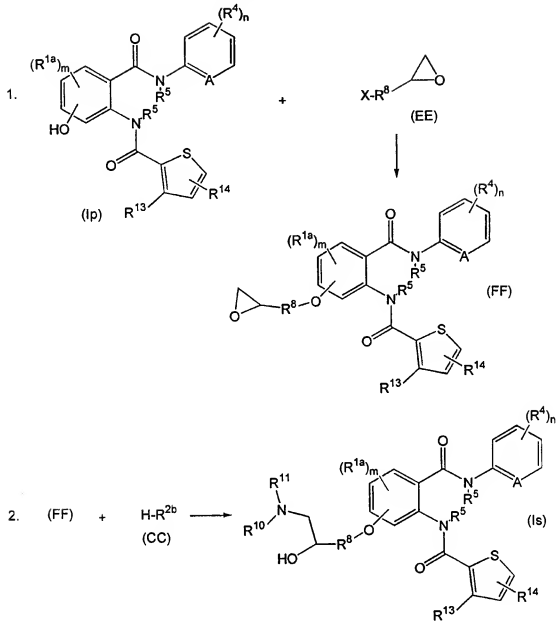
between about -10°C and 10°C, preferably to 0°C. The reaction mixture is then acidified with a mild acid, such as trifluoroacetic acid. The compound of formula (Ir) is then isolated from the reaction mixture by standard isolation techniques, such as purification by HPLC.

Alternatively, compounds of formula (Ir) may be prepared by treating a compound of formula (Ip) in an aprotic solvent, such as DMF, in the presence of a strong base, such as cesium carbonate, at ambient temperature with a compound of formula (DD). The reaction mixture is then heated to between about 50°C and about 65°C, preferably to about 60°C and stirred at that temperature for about 10 to about 20 hours, preferably for about 16 hours. The reaction mixture is then allowed to cool to ambient temperature and filtered. The resulting filtrate is then acidified by a mild acid, such as trifluoroacetic acid, and the compound of formula (Ir) is isolated from the reaction mixture by standard isolation techniques, such as purification by HPLC.

N. Preparation of Compounds of Formula (Is)

Compounds of formula (Is) are compounds of the invention wherein R^2 is $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$ where R^{10} and R^{11} are as defined above in the Summary of the Invention for compounds of formula (I) except that neither can be $-OR^5$, $-S(O)_2-R^{15}$, $-C(O)-R^{15}$, $-C(O)-N(R^5)R^{15}$ or $-C(S)-N(R^5)R^{15}$. They are prepared as illustrated below in Reaction Scheme 14 where A is =CH- or =N-; R^{1a}, R^4 and R^{14} are as described in the Summary of the Invention for compounds of formula (I) except that none can be hydroxy, amino, carboxy or contain a nucleophilic amine; and R^5 and R^8 are as described in the Summary of the Invention for compounds of formula (I); and R^{2b} is $-N(R^{10})R^{11}$ where R^{10} and R^{11} are as defined above; and R^{13} is as described in the Summary of the Invention for compounds of formula (I) except that R^{13} can not be haloalkyl where the alkyl is substituted by only one halogen atom or R^{13} can not contain a nucleophilic nitrogen; and each X is bromo or chloro:

Reaction Scheme 14



Compounds of formula (EE) and (CC) are commercially available or may be prepared according to methods known to those skilled in the art. Compounds of formula (Ip) are prepared herein.

In general, compounds of formula (Is) are prepared by first treating a compound of formula (Ip) in an aprotic solvent, such as DMF, with a compound of formula (EE) in the presence of strong base, such as cesium carbonate. The reaction mixture is stirred at ambient temperature

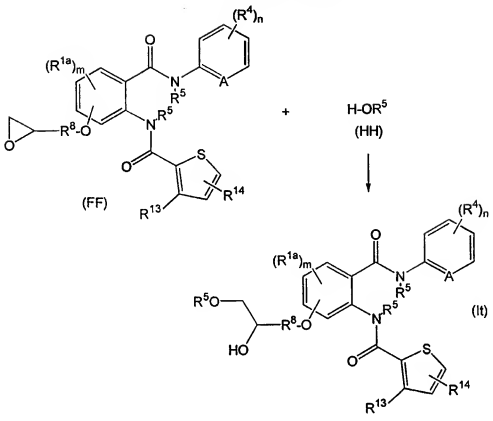
for about 3 days. The compound of formula (FF) is then isolated from the reaction mixture by standard isolation techniques such as filtration and concentration.

The compound of formula (FF) in an aprotic solvent, preferably DMF, is then treated with salt of a compound of formula (CC). The reaction mixture is stirred at ambient temperature for about 16 to about 20 hours, preferably for about 18 hours. The compound of formula (Is) is then isolated from the reaction mixture by standard isolation techniques, such as concentration of volatiles and purification by HPLC.

O. Preparation of Compounds of Formula (It)

Compounds of formula (It) are compounds of the invention wherein R^2 is $-O-R^8-CH(OH)-CH_2-OR^5$ where R^5 and R^8 are as defined in the Summary of the Invention for compounds of formula (I). They are prepared as illustrated in the following Reaction Scheme 15 where A is =CH- or =N-; R^{1a}, R^4 and R^{14} are as described in the Summary of the Invention for compounds of formula (I) except that none can be hydroxy, amino, carboxy or contain a nucleophilic amine; and R^5, and R^8 are as described in the Summary of the Invention for compounds of formula (I); and R^{13} is as described in the Summary of the Invention for compounds of formula (I) except that R^{13} can not be haloalkyl where the alkyl is substituted by only one halogen atom or R^{13} can not contain a nucleophilic nitrogen; and each X is bromo or chloro:

Reaction Scheme 15



Compounds of formula (FF) are prepared herein. Compounds of formula (HH) are commercially available or may be prepared according to methods known to those skilled in the art.

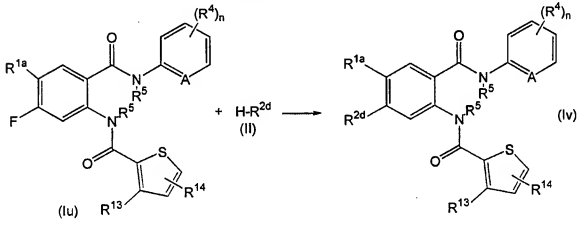
In general, compounds of formula (It) are prepared by treating a compound of formula (FF) in an aprotic solvent, such as methylene chloride, with an excess amount of a compound of formula (HH) in the presence of an oxidant, such as dichlorodicyanobenzoquinone. The reaction mixture is stirred at ambient temperature for about 24 to about 48 hours, preferably for about 48 hours. The reaction is then quenched with the addition of a mild base, such as aqueous sodium bicarbonate. The compound of formula (It) is isolated from the reaction mixture by standard isolation techniques, such as extraction, concentration of volatiles and purification by flash chromatography.

P. Preparation of Compounds of Formula (Iv)

Compounds of formula (Iv) are compounds of the invention wherein the R^2 substituent is

in the 4-position and is -S-R^9, -N(R^{10})R^{11}, -N(R^5)-R^8-N(R^{10})R^{11}, -S-R^8-N(R^5)R^6, -S-R^8-C(O)OR^5, or -N(R^5)-CH(R^{12})-C(O)OR^5 (where R^5, R^6, R^8, R^9 and R^{12} are as defined in the Summary of the Invention for compounds of formula (I) and R^{10} and R^{11} are as defined in the Summary of the Invention for compounds of formula (I) except that neither can be -OR^5, -S(O)$_2$-R^{15}, -C(O)-R^{15}, -C(O)N(R^5)R^{15} or -C(S)-N(R^5)R^{15} when R^2 is -N(R^{10})R^{11}). They are prepared as illustrated below in Reaction Scheme 16 wherein R^{1a} is halo; and R^4 and R^{14} are as described in the Summary of the Invention for compounds of formula (I) except that neither can contain a nucleophilic amine; and R^5 is as described in the Summary of the Invention for compounds of formula (I); and R^{13} is as described in the Summary of the Invention for compounds of formula (I) except that R^{13} can not be haloalkyl where the alkyl is substituted by only one halogen atom or R^{13} can not contain a nucleophilic nitrogen; and R^{2d} is -S-R^8, -N(R^{10})R^{11}, -N(R^5)-R^8-N(R^{10})R^{11}, -S-R^8-N(R^5)R^6, -S-R^8-C(O)OR^5, or -N(R^5)-CH(R^{12})-C(O)OR^5 (where R^5, R^6, R^8, R^9, R^{10}, R^{11} and R^{12} are as defined above for R^2):

Reaction Scheme 16



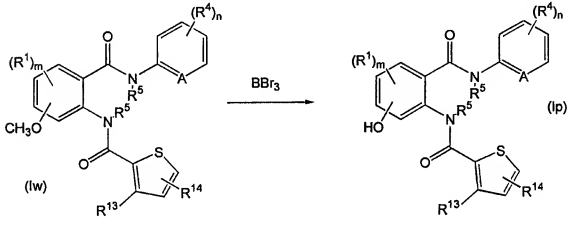
Compounds of formula (II) are commercially available, or may be prepared according to methods known to those skilled in the art. Compounds of formula (Iu) may be prepared according to methods disclosed herein.

In general, compounds of formula (Iv) are prepared by treating a compound of formula (Iu) with a compound of formula (II) in the presence of a base. The reaction mixture is heated to temperatures of between about 80°C and about 105°C, preferably at about 85°C, for about 10 to about 20 hours, preferably for about 15 hours. The compound of formula (Iv) is then isolated from the reaction mixture by standard isolation techniques, such as concentration and purification by HPLC.

Q. Preparation of Compounds of Formula (Ip)

Compounds of formula (Ip) are compounds of the invention wherein R^2 is hydroxy. These compounds are prepared as illustrated below where A is =CH- or =N-; and R^1, R^4, R^5, R^{13}, R^{14}, m and n are as defined above in the Summary of the Invention for compounds of formula (I):

Reaction Scheme 17



Compounds of formula (Iw) are compounds of the invention which are prepared by the methods disclosed herein.

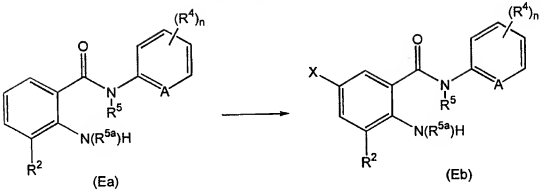
In general, compounds of formula (Ip) are prepared by treating a compound of formula (Iw) in an aprotic solvent, such as methylene chloride, with boron tribromide at ambient temperature. The reaction mixture is stirred for about 10 to about 20 hours, preferably for about 18 hours. The compound of formula (Ip) is then isolated from the reaction mixture by standard isolation techniques, such as extraction and concentration.

During this reaction, if any of the other substituents, such as R^1, R^4, etc., contain an ester group or a lower alkyl ether group , the ester group will also be hydrolyzed to the corresponding acid and the ether group will be hydrolyzed to the corresponding alcohol.

R. Preparation of Compounds of Formula (Eb)

Compounds of formula (Eb) are compounds of formula (E) wherein R^{1a} is in the 5-position and is halo. These compounds, which are intermediates in the preparation of the compounds of the invention, may be prepared as illustrated below in Reaction Scheme 18 where A is =CH- or =N-; R^2, R^4, and R^5 are as described above in the Summary of the Invention for compounds of formula (I); and R^{5a} is hydrogen, and X is chloro or bromo:

Reaction Scheme 18



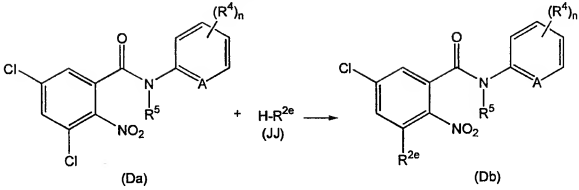
Compounds of formula (Ea) are prepared by methods disclosed herein.

In general, compounds of formula (Eb) are prepared by treating a compound of Ea in an organic solvent, such as benzene, with a halogenating agent. The reaction mixture is heated to temperatures of about 45°C to about 55°C, preferably to about 50°C to about 55°C. The reaction mixture is allowed to cool to ambient temperature and the compound of formula (Eb) is then isolated from the reaction mixture by standard isolation techniques, such as concentration, extraction and recrystallization.

S. Preparation of Compounds of Formula (Db)

Compounds of formula (Db) are compounds of formula (D) where the R^{1a} substituent is in the 5-position and is chloro and R^2 is in the 3-position and is $-N(R^{10})R^{11}$, $-N(R^5)-R^8-N(R^{10})R^{11}$, $-N(R^5)-CH(R^{12})-C(O)OR^5$ (where R^5, R^8, R^{10}, R^{11} and R^{12} are as defined in the Summary of the Invention for compounds of formula (I) except that R^{10} and R^{11} can not be $-S(O)_2-R^{15}$, $-C(O)-R^{15}$, $-C(O)N(R^5)R^{15}$ or $-C(S)N(R^5)R^{15}$ when R^2 is $-N(R^{10})R^{11}$). These compounds, which are intermediates in the preparation of the compounds of the invention, are prepared as illustrated below in Reaction Scheme 19 where A is =CH- or =N-; R^4 and R^5 are as described in the Summary of the Invention for compounds of formula (I); and R^{2a} is $-N(R^{10})R^{11}$, $-N(R^5)-R^8-N(R^{10})R^{11}$, or $-N(R^5)-CH(R^{12})-C(O)OR^5$ (where R^5, R^8, R^{10}, R^{11}, and R^{12} are as defined above for R^2):

Reaction Scheme 19



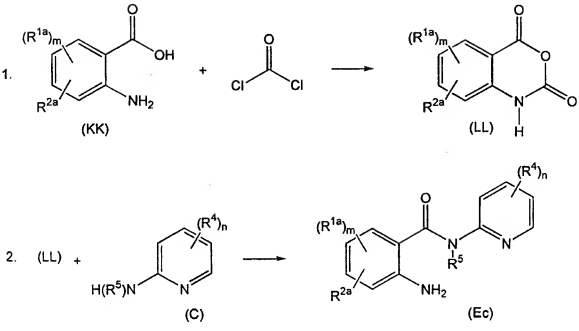
Compounds of formula (Da) are prepared by methods described herein. Compound of formula (JJ) are commercially available or may be prepared according to methods known to those skilled in the art.

In general, compounds of formula (Db) are prepared by treating a compound of formula (Da) in a polar aprotic solvent, such as DMSO, with a compound of formula (JJ) in the presence of a base, such as diisopropylethylamine. The reaction mixture is heated to temperatures of between about 100°C to about 120°C, preferably to about 110°C to about 120°C and maintained at that temperature for about 3 to about 5 hours, preferably for about 4 hours. The reaction mixture is then cooled to ambient temperature and the compound of formula (Db) is isolated from the reaction mixture by standard isolation techniques such as extraction, concentration and purification by flash chromatography.

T. Preparation of Compounds of Formula (Ec)

Compounds of formula (Ec) are compounds of formula (E) where R^{5a} is hydrogen. These compounds, which are intermediates in the preparation of the compounds of the invention, may be prepared as illustrated below in Reaction Scheme 20 where A is =CH- or =N-; R^{1a} is hydrogen, alkyl, aryl, aralkyl, halo, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-C(O)-N(R^5)R^6$ and $-N(R^5)R^6$ (where each R^5 and R^6 can not be hydrogen and R^9 is alkyl, aryl, or aralkyl); and R^{2a} is as defined above in Reaction Scheme 1, and R^4 and R^5 are as defined above in the Summary of the Invention for compounds of formula (I):

Reaction Scheme 20



Compounds of formula (KK) and formula (C) and phosgene are commercially available or may be prepared according to methods known to those skilled in the art.

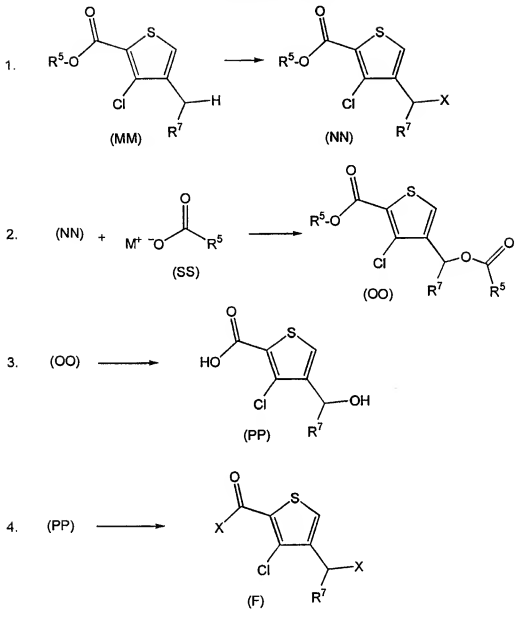
In general, compounds of formula (Ec) are prepared by first treating a compound of formual (KK) with phosgene in an aprotic solvent, such as dioxane. The reaction mixture is stirred at ambient temperature to about 70°C, preferably at about 65°C, for about 8 to about 12 hours, preferably for about 10 hours. The reaction mixture is cooled to ambient temperature and the compound of formula (LL) is then isolated from the reaction mixture by standard isolation techniques, such as filtration and evaporation of solvents.

The compound of formula (LL) in a polar aprotic solvent, such as dioxane, is treated with a compound of formula (C). The reaction mixture is heated at reflux for about 10 to about 20 hours, preferably for about 15 hours. The reaction mixture is allowed to cool to ambient temperature and the compound of formula (Ec) is then isolated from the reaction mixture by standard isolation techniques, such as filtration and concentration.

U. Preparation of Compounds of Formula (F)

Compounds of formula (F) are intermediates used to prepare compounds of the invention and may be prepared as illustrated below in Reaction Scheme 21 wherein each R^5 is alkyl, R^7 is hydrogen or alkyl; and M is a metal cation and X is bromo or chloro:

Reaction Scheme 21



Compounds of formula (MM) are commercially available or may be prepared according to methods disclosed herein or by standard methods known to those of ordinary skill in the art.

In general, compounds of formula (F) are prepared by first treating a compound of formula (MM) in a similar manner as that described herein for the preparation of compounds of formula (W) to prepare a compound of formula (NN).

The compound of formula (NN) in a mild acidic aqueous solution is then treated with a compound of formula (SS). The reaction mixture is heated to reflux for about 20 hours to about

30 hours, preferably for about 24 hours. The reaction mixture is then cooled to ambient temperature and the compound of formula (OO) is then isolated from the reaction mixture by standard isolation techniques, such as concentration and extraction.

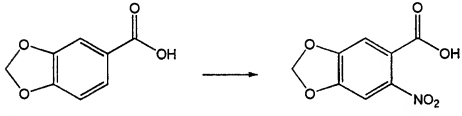
The compound of formula (OO) is then hydrolyzed under standard basic conditions to produce the compound of formula (PP). The compound of formula (PP) may be isolated as the metal salt and may be used as such in the next step.

The compound of formula (PP) is then converted to the acid halide by treatment with the appropriate agent, such as thionyl chloride or thionyl bromide. The resulting compound of formula (F) is isolated from the reaction mixture by standard isolation techniques.

V. Preparation of the Compound of Formula (RR)

The compound of formula (RR) is an intermediate in the preparation of compounds of the invention and is prepared as illustrated below in Reaction Scheme 22:

Reaction Scheme 22



(QQ) (RR)

The compound of formula (QQ) is commercially available.

In general, the compound of formula (RR) is prepared by treating the compound of formula (QQ) in the presence of a mild acid, such as trifluoroacetic acid, with nitric acid. The reaction mixture is stirred at temperatures of between about -10°C and 10°C, preferably at about 0°C, for about 30 minutes to an hour, preferably for about 1 hour. The reaction mixture is warmed to ambient temperature and stirred for about 2 to about 4 hours, preferably for about 3 hours. The compound of formula (RR) is then isolated from the reaction mixture by standard isolation techniques, such as precipitation and filtration.

All compounds of the invention as prepared above which exist in free base or acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid. Salts of the compounds prepared above may be converted to their free base or acid form by standard techniques.

*****

The following specific preparations and examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

PREPARATION 1

Compounds of Formula (B)

A. To a suspension of 5-chloro-2-nitrobenzoic acid (21g, 100 mmol) in dry methylene chloride (200 mL) at 0°C were added several drops of DMF, followed by oxalyl chloride (13 mL, 150 mmol). The reaction was warmed to ambient temperature. After 16 hours the solvents were removed and the viscous oil dried *in vacuo* to afford 23 g (quantitative yield) of 5-chloro-2-nitrobenzoyl chloride; NMR ($CDCl_3$) 8.1 (d, 1), 7.7 (m, 2) ppm.

B. In a similar manner, the following compounds were made:

3,5-dichloro-2-nitrobenzoyl chloride;

5-methyl-2-nitrobenzoyl chloride;

5-(chloro)carbonyl-6-nitro-1,3-benzodioxole;

3-methoxy-2-nitrobenzoyl chloride; and

4,5-dimethoxy-2-nitrobenzoyl chloride.

C. In a similar manner, other compounds of formula (B) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 2

Compounds of Formula (D)

A. To a solution of 5-chloro-2-nitrobenzoyl chloride (23 g, 100 mmol) in methylene chloride (200 mL) at 0°C was added triethylamine (16 mL, 115 mmol), followed by 4-chloroaniline (14g, 110 mmol). The mixture was stirred for 20 minutes at 0°C, then warmed to ambient temperature. After 5 hours, the mixture was concentrated of all volatiles *in vacuo*. The residual solid was dissolved in ethyl acetate (400 mL) and washed with water (200 mL), 1M hydrochloric acid (2x200 mL), 1M sodium bicarbonate (200 mL) and brine (200 mL) and dried over $MgSO_4$. Concentration and drying *in vacuo* afforded 30 g (93% yield) of *N*-(4-chlorophenyl)-5-chloro-2-nitrobenzamide; NMR ($CDCl_3$) 8.1 (d, 1), 7.7 (br, 1), 7.6 (m, 2), 7.5 (d, 2), 7.3 (d, 2) ppm.

B. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-3,5-dichloro-2-nitrobenzamide; NMR ($CDCl_3$) 8.4 (s, 1), 8.0-8.2 (m, 3), 7.9 (m, 1) ppm;

N-(4-chlorophenyl)-4,5-dimethoxy-2-nitrobenzamide; NMR (DMSO-d_6/TFA) 10.6 (s, 1), 7.7 (d, 2), 7.6 (s, 1), 7.4 (d, 2), 7.2 (s, 1), 4.0 (s, 3), 3.9 (s, 3) ppm;

N-(4-chlorophenyl)-3-methoxy-2-nitrobenzamide; NMR (DMSO-d_6/TFA) 10.8 (s, 1), 7.7 (m, 3), 7.5 (d, 1), 7.4 (t, 2), 3.9 (s, 3), 3.4 (br s, 1) ppm;

N-(5-chloropyridin-2-yl)-3-methoxy-2-nitrobenzamide; NMR ($CDCl_3$) 8.8 (br, 1), 8.3 (d, 1), 8.1 (s, 1), 7.7 (d, 1), 7.5 (t, 1), 7.3 (m, 2), 3.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-5-chloro-2-nitrobenzamide;

N-(5-bromopyridin-2-yl)-5-chloro-2-nitrobenzamide;

N-(4-chlorophenyl)-5-methyl-2-nitrobenzamide;

N-(4-bromophenyl)-5-methyl-2-nitrobenzamide;

N-(pyridin-2-yl)-5-chloro-2-nitrobenzamide;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-nitro-1,3-benzodioxole; and

N-(4-chlorophenyl)-3-nitro-pyridin-2-amide.

C. In a similar manner, other compounds of formula (D) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 3

Compounds of Formula (E)

A. *N*-(4-Chlorophenyl)-5-chloro-2-nitrobenzamide (13.2 g, 42.4 mmol) and tin(II) chloride dihydrate (48 g, 213 mmol) were combined in ethyl acetate (90 mL) and the mixture was heated at 70°C under a nitrogen atmosphere. After 15 minutes, the mixture was cooled to ambient temperature, then poured onto water (750 mL) and ethyl acetate (750 mL). The aqueous layer was adjusted to pH 8 with by addition of 1 N NaOH and a saturated $NaHCO_3$ solution, and the layers were separated. The aqueous layer was further extracted with 500 mL of ethyl acetate. The combined organic extracts were washed with water (1 L), then brine (500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 11.6 g (97% yield) of *N*-(4-chlorophenyl)-2-amino-5-chlorobenzamide as an off-white solid; NMR ($CDCl_3$) 7.7 (br s, 1), 7.2-7.5 (m, 6), 6.7 (d, 1), 5.5 (br s, 2) ppm.

B. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2,3-diamino-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.6 (s, 1), 8.4 (dd, 1), 8.0 (dd, 1), 7.8 (m, 1), 7.8 (d, 1), 7.2 (dd, 1), 7.1 (m, 1), 6.8 (d, 1), 6.5 (s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-amino-3-dimethylamino-5-chlorobenzamide; NMR ($CDCl_3$) 8.5 (s, 1), 8.3 (d, 1), 8.2 (d, 1), 7.7 (dd, 1), 7.3 (d, 1), 7.1 (d,1), 6.0 (br s, 2), 2.7 (s, 6) ppm;

N-(5-chloropyridin-2-yl)-2-amino-3-(morpholin-4-yl)-5-chlorobenzamide; NMR ($CDCl_3$) 8.3 (m, 1), 7.5 (m, 1), 7.1-7.4 (m, 3), 3.9 (m, 4), 3.2 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-amino-5-chlorobenzamide;

N-(5-bromopyridin-2-yl)-2-amino-5-chlorobenzamide;
N-(4-chlorophenyl)-2-amino-5-methylbenzamide;
N-(4-bromophenyl)-2-amino-5-methylbenzamide;
N-(5-chloropyridin-2-yl)-2-amino-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide;
N-(4-chlorophenyl)-2-amino-5-chloro-3-(morpholin-4-yl)benzamide;
N-(5-chloropyridin-2-yl)-2-amino-3-(4-ethylpiperazin-1-yl)-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-amino-3-(4-(ethoxycarbonylpiperidin-1-yl)-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-amino-5-(*N'*-methyl-*N'*-(ethoxycarbonylmethyl)amino)-3-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-amino-3-(*N',N'*-di(2-methoxyethyl)amino)-5-chlorobenzamide;
N-(5-chloropyridin-2-yl)-2-amino-3-(pyrrolidin-1-yl)-5-chlorobenzamide;
5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-amino-1,3-benzodioxole.

C. In a manner similar to that described in Paragraph A above, *N*-(5-chloropyridin-2-yl)-2-nitro-3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-chlorobenzamide (13 g, 26 mmol) was reacted with tin(II) chloride dihydrate (29 g, 130 mmol) in pyridine (100 mL) to afford 7.1 g (60% yield) of *N*-(5-chloropyridin-2-yl)-2-amino-3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-chlorobenzamide, as a yellow solid; NMR (DMSO-d_6) 10.8 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.6 (d, 1), 7.1 (d, 1), 6.2 (d, 2), 3.3 (m, 4), 2.7 (br, 4), 1.4 (s, 9) ppm.

D. To a solution of sodium hydrosulfite (300 g, 1.7 mol) in water (4 L) was added *N*-(5-chloropyridin-2-yl)-2-nitro-3-methoxybenzamide (140 g, 0.45 mol). Tetrahydrofuran (2 L) and 1,4-dioxane (2 L) were added and the resulting mixture stirred at ambient temperature. After 16 hours, the solution was made basic by addition of potassium carbonate and the phases separated. The organic phase was concentrated of all volatiles *in vacuo* to give an off-white solid. The solid was washed with water, filtered, and dried under vacuum to afford 111 g (88% yield) of *N*-(5-chloropyridin-2-yl)-2-amino-3-methoxybenzamide; NMR ($CDCl_3$) 8.8 (br, 1), 8.3 (d, 1), 8.1 (s, 1), 7.7 (dd, 1), 7.1 (dd, 1), 6.8 (d, 1), 6.6 (t, 1), 5.9 (br, 1), 3.9 (s, 3) ppm.

E. In a similar manner, the following compound was made:
N-(4-chlorophenyl)-2-amino-3-methoxybenzamide.

F. To a suspension of *N*-(4-bromophenyl)-2-nitro-5-chlorobenzamide (0.50 g, 1.4 mmol) in methanol (20 mL) was added 5% platinum on carbon (Degussa type, 50% water, 0.20 g), and the mixture stirred under hydrogen (balloon). After 0.5 hours, the mixture was filtered and concentrated of all volatiles *in vacuo* to afford 0.45 g (99% yield) of *N*-(4-bromophenyl)-2-amino-5-chlorobenzamide as a white solid; NMR (DMSO-d_6) 10.2 (s, 1), 7.5-7.7 (m, 5), 7.2 (dd, 1), 6.8 (d, 1) ppm.

G. In a similar manner, the following compounds were made:

N-phenyl-2-amino-4,5-dimethoxybenzamide;
N-(5-chloropyridin-2-yl)-2-amino-5-methylbenzamide;
N-phenyl-2-amino-5-methylbenzamide;
N-(4-chlorophenyl)-3-aminopyridin-2-amide.

H. In a manner similar to those methods described above, other compounds of formula (E) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 4

Compounds of Formula (G)

A. To a solution of 3-chloro-4-chloromethyl-2-(chlorocarbonyl)thiophene (3.1 g, 13.5 mmol) in methylene chloride (40 mL) at 0°C was added *N*-(4-chlorophenyl)-2-amino-5-chlorobenzamide (3.8 g, 13.5 mmol), followed after 5 minutes by pyridine (1.6 mL, 16 mmol). The mixture was warmed to ambient temperature. After 17 hours, the mixture was concentrated of all volatiles *in vacuo*. The resulting solid was triturated with water and a small amount of acetonitrile and dried *in vacuo* to afford 5.1 g (80% yield) of *N*-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide as a tan powder: NMR (DMSO-d_6) 11.1 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 7.9 (s, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.4 (d, 2), 4.8 (s, 2) ppm.

B. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCl_3$) 9.3 (br, 1), 9.1 (br, 1), 8.3 (d, 1), 8.0 (d, 1), 7.7 (d, 1), 7.6 (s, 1), 7.2 (d, 1), 7.0 (d, 1), 4.6 (s, 2), 3.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide; NMR ($CDCl_3$) 10.9 (s, 1), 9.5 (s, 1), 8.4 (s, 1), 7.8-8.2 (m, 3), 7.4 (m, 2), 4.7 (s, 2), 3.7 (m, 4), 2.9 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide; NMR ($CDCl_3$) 10.8 (s, 1), 9.5 (s, 1), 8.4 (s, 1), 7.8-8.2 (m, 3), 7.4 (m, 2), 4.7 (s, 2), 3.4 (m, 8), 2.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-ethylpiperazin-1-yl)-5-chlorobenzamide; NMR ($CDCl_3$) 10.7 (s, 1), 9.6 (s, 1), 8.3 (s, 1), 7.8-8.2 (m, 3), 7.5 (m, 2), 4.6 (s, 2), 3.2-3.5 (m, 10), 1.4 (m, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-(ethoxycarbonyl)piperidin-1-yl)-5-chlorobenzamide; NMR ($CDCl_3$) 10.8 (s, 1), 9.5 (s, 1),

7.1-8.4 (m, 6), 4.5 (s, 2), 3.0-3.5 (m, 7), 1.8-2.2 (m, 4), 1.2 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-chloro-5-(*N*-methyl-*N*-(ethoxycarbonyl)methylamino)benzamide; NMR ($CDCl_3$) 10.9 (s, 1), 9.5 (s, 1), 8.5 (s, 1), 7.8-8.2 (m, 3), 7.5 (m, 2), 4.6 (s, 2), 3.0-3.6 (m, 4), 2.9 (s, 3), 1.1 (t, 3);

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(*N*',*N*'-di(2-methoxyethyl)amino)-5-chlorobenzamide; NMR ($CDCl_3$) 10.8 (s, 1), 9.5 (s, 1), 7.3-8.6 (m, 6), 4.4 (s, 2), 2.8-3.5 (m, 11) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-amino-5-chlorobenzamide; NMR ($CDCl_3$) 10.9 (s, 1), 9.7 (s, 1), 7.4-8.6 (m, 6), 4.2 (s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.4 (s, 1), 11.0 (s, 1), 7.6-8.4 (m, 7), 4.8 (s, 2) ppm;

N-(4-chlorophenyl)-2-[((4,5-di(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.2 (s, 1), 10.7 (s, 1), 8.3 (d, 1), 7.4-7.9 (m, 6), 5.1 (s, 2), 4.8 (s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-dimethylamino-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.5 (s, 1), 9.6 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 2), 7.8 (dd, 1), 7.7 (d, 1), 4.6 (s, 2), 3.0 (s, 6) ppm;

N-(pyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.6 (s, 1), 8.4 (d, 1), 8.3 (t, 1), 8.0 (d, 1), 7.9 (s, 1), 7.8 (s, 1), 7.7 (d, 1), 7.6 (dd, 1), 7.5 (t, 1), 4.6 (s, 2) ppm;

N-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(pyrrolidin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-chlorobenzamide;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole;

N-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-fluorobenzamide;

N-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.4 (s, 1), 9.5 (s, 1), 8.1 (s, 1), 7.7 (d, 2), 7.3-7.4 (m, 4), 4.8 (s, 2), 3.9 (s, 3) ppm.

C. In a manner similar to those methods described above, other compounds of formula (G) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 5

Compounds of Formula (K)

A. To a suspension of *N*-(4-chlorophenyl)-2-[((5-methyl-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide (2.6 g, 6.0 mmol) in dry benzene (250 mL) were added N-bromosuccinimide (1.2 g, 6.6 mmol) and benzoyl peroxide (0.15 g, 0.6 mmol). The mixture was refluxed while irradiating with a 250 Watt lamp. After 28 hours the reaction was concentrated of all volatiles *in vacuo* and the resulting solid triturated with benzene. Purification by flash chromatography on silica gel afforded 2.3 g (75% yield) of *N*-(4-chlorophenyl)-2-[((5-bromomethyl-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide as a white solid; NMR (DMSO-d_6) 11.1 (s, 1), 10.7 (s, 1), 8.3 (d, 1), 7.9 (s, 1), 7.7 (d, 2), 7.6 (d, 1), 7.4 (d, 2), 7.3 (s, 1), 4.9 (s, 2) ppm.

B. In a similar manner, the following compounds were made:

N-(4-chlorophenyl)-2-[((3-(bromomethyl)benzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.4 (s, 1), 10.8 (s, 1), 8.4 (d, 1), 7.4-8.2 (m, 10), 5.3 (s, 2) ppm;

N-(4-chlorophenyl)-2-[((6-(bromomethyl)benzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.4 (s, 1), 10.8 (s, 1), 8.4 (d, 1), 7.4-8.2 (m, 10), 4.9 (s, 2) ppm.

C. In a similar manner, other compounds of formula (K) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 6

Compounds of Formula (T)

A. A mixture of 3,3,3-trifluoropropyl bromide (10.0 g, 56.5 mmol), potassium cyanide (5.2 g, 79.8 mmol), tetrabutylammonium iodide (0.1 g, 0.3 mmol) and DMSO (10 mL) was heated at 60°C for 15 hours. After cooling, the mixture was extracted with ethyl ether (80 mL) and water (100 mL). The organic layer was washed with water (3x100 mL), dried

(Na_2SO_4) and filtered. Ethanol (10mL) was added, and the solution was cooled to 0°C, and saturated with HCl gas. The vessel was sealed and allowed to stand at ambient temperature for 15 hours. The mixture was then added to a solution of hexane (200 mL) and ethyl ether (40 mL). The precipitate was collected and dried *in vacuo* to give 3.2 g of ethyl (2,2,2-trifluoroethyl)acetimidate hydrochloride; NMR (DMSO-d_6/TFA) 4.4 (q, 3), 2.9 (t, 2) 2.6 (m, 2), 1.3 (t, 3) ppm.

B. In a similar manner, other compounds of formula (T) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 7

Compounds of Formula (W)

A. To 2-methoxycarbonyl-3-chloro-4-methylthiophene (100 g, 0.53 mol) in dry carbon tetrachloride (1.5 L) were added sulfuryl chloride (65 mL, 0.81 mol) and benzoyl peroxide (2.5 g, 10 mmol). The reaction was heated at reflux for 17 hours, then cooled to ambient temperature and concentrated of all volatiles *in vacuo*. Purification of the resulting oil by flash chromatography on silica gel afforded 63 g (54% yield) of 2-methoxycarbonyl-3-chloro-4-(chloromethyl)thiophene as a yellow oil which crystallized to fine needles upon standing; NMR ($CDCl_3$) 7.6 (s, 1), 4.6 (s, 2), 3.9 (s, 3) ppm.

B. To 2-methoxycarbonyl-3-chloro-4-methylthiophene (0.25 g, 1.3 mmol) in dry benzene (25 mL) were added *N*-bromosuccinimide (0.28 g, 1.6 mmol) and benzoyl peroxide (0.03 g, 0.13 mmol). The mixture was refluxed while irradiating with a 250 Watt lamp. After 2 hours the reaction was cooled and concentrated of all volatiles *in vacuo*. Purification by flash chromatography on silica gel afforded 0.20 g (58% yield) of 2-methoxycarbonyl-3-chloro-4-(bromomethyl)thiophene as a white solid; NMR ($CDCl_3$) 7.6 (s, 1), 4.4 (s, 2), 3.9 (s, 3) ppm.

C. In a similar manner, other compounds of formula (W) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 8

Compounds of Formula (X)

A. To 2-methoxycarbonyl-3-chloro-4-(bromomethyl)thiophene (0.20 g, 0.74 mmol) in methylene chloride (7.5 mL) was added 1-methylpiperazine (0.095 mL, 0.86 mmol) and the mixture was stirred at ambient temperature. After 16 hours, the mixture was poured onto methylene chloride (20 mL) and washed with dilute aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel

afforded 0.085 g (40% yield) of 2-methoxycarbonyl-3-chloro-4-((4-methylpiperazin-1-yl)methyl)thiophene as a tan solid; NMR ($CDCl_3$) 7.4 (s, 1), 3.9 (s, 3), 3.5 (s, 2), 2.3-2.7 (br m, 8), 2.2 (s, 3) ppm.

B. In a similar manner, the following compounds were made:
2-methoxycarbonyl-3-chloro-4-((morpholin-4-yl)methyl)thiophene;
2-methoxycarbonyl-3-chloro-4-((thiomorpholin-4-yl)methyl)thiophene.

C. In a similar manner, other compounds of formula (X) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 9

Compounds of Formula (Y)

A. To a solution of 2-methoxycarbonyl-3-chloro-5-methylthiophene (1.3g, 6.8 mmol) in ethanol (16 mL) was added aqueous sodium hydroxide (1 N, 16 mL, 16 mmol) and the mixture stirred at ambient temperature. After 3 hours the mixture was concentrated of all volatiles *in vacuo*. The residual solid was dissolved in water (60 mL), acidified with 1 N HCl and the solid collected by filtration to afford 1.2 g (95% yield) of 2-carboxy-3-chloro-5-methylthiophene as a white solid; NMR ($CDCl_3$) 6.8 (s, 1), 2.5 (s, 3) ppm.

B. In a similar manner, the following compounds were made:
2-carboxy-3-methoxybenzo[*b*]thiophene;
2-carboxy-3-chloro-4-((4-methylpiperazin-1-yl)methyl)thiophene, hydrochloride salt;
2-carboxy-3-chloro-4-cyanothiophene.

C. In a similar manner, other compounds of formula (Y) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 10

Compounds of Formula (FF)

A. To a solution of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide (4.5 g, 8.0 mmol) in DMF (200 mL) was added cesium carbonate (18 g, 55 mmol), followed by epibromohydrin (1.4 mL, 16 mmol). The mixture was stirred at ambient temperature for 3 days, then filtered. The filtrate was concentrated *in vacuo* to afford a quantitative yield of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(methylsulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2,3-epoxypropoxy)-5-chlorobenzamide; NMR ($CDCl_3$) 9.2 (s, 1), 8.8 (s, 1), 8.2 (d, 1), 8.1 (s, 1), 7.7 (d, 1), 7.6 (s, 1),

7.3 (s, 1), 7.1 (s, 1), 4.4 (d, 1), 4.3 (s, 2), 4.0 (m, 1), 3.4 (br m, 1), 3.0 (br m, 1), 2.9 (s, 3), 2.8 (s, 3), 2.7 (br m, 1) ppm.

B. In a similar manner, the following compound was made: *N*-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((dimethylamino)sulfonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(2,3-epoxypropoxy)-5-chlorobenzamide.

C. In a similar manner, other compounds of formula (FF) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 11

Compounds of Formula (Eb)

A. To *N*-(5-chloropyridin-2-yl)-2-amino-3-methoxybenzamide (39 g, 140 mmol) in benzene (2 L) was added *N*-chlorosuccinimide (20 g, 148 mmol) and the reaction heated at 50-55°C. After 24 hours the reaction was cooled to ambient temperature and concentrated of all volatiles *in vacuo*. The resulting solid was dissolved in ethyl acetate (1 L), washed with water (3x100 mL), dried over sodium sulfate, and concentrated. Recrystallization from benzene afforded 40 g (90% yield) of *N*-(5-chloropyridin-2-yl)-2-amino-3-methoxy-5-chlorobenzamide as off-white needles; NMR ($CDCl_3$) 8.6 (br, 1), 8.3 (m, 2), 7.7 (dd, 1), 7.1 (d, 1), 6.8 (d, 1), 5.9 (br, 1), 3.9 (s, 3) ppm.

B. In a similar manner, the following compound was made: *N*-(4-chlorophenyl)-2-amino-3-methoxy-5-chlorobenzamide.

C. To a solution of *N*-(4-chlorophenyl)-2-amino-3-methylbenzamide (0.40 g, 1.5 mmol) in chloroform (3 mL) at 0°C was added SO_2Cl_2 (0.3 1g, 2.3 mmol). The mixture was warmed to ambient temperature and stirred for 1 hour. Concentration of all volatiles *in vacuo* afforded *N*-(4-chlorophenyl)-2-amino-3-methyl-5-chlorobenzamide as a yellow solid; NMR (DMSO-d_6) 10.2 (s, 1), 7.8 (d, 2), 7.6 (s, 1), 7.4 (d, 2), 7.2 (s, 1), 6.2 (br, 2), 2.1 (s, 3) ppm.

D. In a similar manner, the following compound was made: *N*-(4-chlorophenyl)-2-amino-4-fluoro-5-chlorobenzamide.

E. In a manner similar to those methods described above, other compounds of formula (Eb) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 12

Compounds of Formula (Db)

A. To a solution of *N*-(5-chloropyridin-2-yl)-2-nitro-3,5-dichlorobenzamide (12 g,

34 mmol) in DMSO (50 mL) was added morpholine (3.6 g, 41 mmol) followed by *N,N*-diisopropylethylamine (8.9 g, 69 mmol). The mixture was heated at 110-120°C for 4 hours, then cooled to ambient temperature, quenched with water (50 mL) and extracted with ethyl acetate (3x100 mL). The combined organics were washed with brine (2x30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel afforded 6.3 g (46% yield) of *N*-(5-chloropyridin-2-yl)-2-nitro-3-(morpholin-4-yl)-5-chlorobenzamide; NMR ($CDCl_3$) 8.2 (m, 1), 7.7 (m, 1), 7.2-7.4 (m, 3), 3.8 (m, 4), 3.0 (m, 4) ppm.

B. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-nitro-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 9.8 (br s, 1), 8.4 (d, 1), 8.0 (d, 1), 7.8 (dd, 1), 7.6 (d, 2), 3.4 (d, 2), 3.3 (d, 2), 3.2 (m, 4), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-nitro-3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-chlorobenzamide; NMR (DMSO-d_6) 11.5 (br, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.7 (s, 1), 7.6 (d, 1), 3.4 (br, 4), 2.9 (m, 4), 1.4 (s, 9) ppm;

N-(4-chlorophenyl)-2-nitro-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-nitro-3-(4-ethylpiperazin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-nitro-3-(4-(ethoxycarbonyl)piperidin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-nitro-3-chloro-5-(*N'*-methyl-*N'*-(ethoxycarbonyl)methylamino)benzamide;

N-(5-chloropyridin-2-yl)-2-nitro-3-(*N',N'*-di(2-methoxyethyl)amino)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-nitro-3-(pyrrolidin-1-yl)-5-chlorobenzamide.

C. Into a solution of *N*-(5-chloropyridin-2-yl)-2-nitro-3,5-dichlorobenzamide (4.0 g, 12 mmol) in dimethyl sulfoxide (60 mL) was bubbled an excess of dimethyl amine gas. The mixture was sealed in a pressure tube and heated at 50°C. After 3 hours, the mixture was cooled to ambient temperature, then poured into water, and extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo* to afford 3.8 g (93% yield) of *N*-(5-chloropyridin-2-yl)-2-nitro-3-dimethylamino-5-chlorobenzamide; NMR ($CDCl_3$) 9.6 (s, 1), 8.2 (d, 1), 7.8 (d, 1), 7.7 (dd, 1), 7.1 (d, 1), 6.9 (d,1), 2.8 (s, 6) ppm.

D. In a similar manner, the following compound was made:

N-(5-chloropyridin-2-yl)-2-nitro-3-amino-5-chlorobenzamide.

E. In a manner similar to those methods described above, other compounds of formula (Db) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 13

Compounds of Formula (LL)

A. A mixture of anthranilic acid (10 g, 73 mmol), and phosgene (1.9 M solution in toluene, 50 mL, 94 mmol) in 1,4-dioxane (120 mL) was stirred at ambient temperature. After 50 hours, the mixture was heated at 65°C for 10 hours then cooled to ambient temperature. The solid was collected by filtration, washed with ethyl ether and dried *in vacuo* to afford 11g (92% yield) of benzoxazine-2,4-dione as tan solid; NMR (DMSO-d_6) 11.7 (s, 1), 7.9 (d, 1), 7.7 (t, 1), 7.2 (t, 1), 7.1 (d, 1) ppm.

B. In a similar manner, the following compounds were made:
6,7-difluorobenzoxazine-2,4-dione; NMR (DMSO-d_6) 11.9 (s, 1), 8.0 (t, 1), 7.0 (dd, 1) ppm;
6-fluorobenzoxazine-2,4-dione;
7-fluorobenzoxazine-2,4-dione;
8-methylbenzoxazine-2,4-dione;
7-azabenzoxazine-2,4-dione.

C. In a similar manner, other compounds of formula (LL) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 14

Compounds of Formula (Ec)

2-Amino-(*N*-4-chlorophenyl)benzamide

A. A mixture of benzoxazine-2,4-dione (1.6 g, 10 mmol) and 4-chloroaniline (2.5 g, 20 mmol) in 1,4-dioxane (30 mL) was heated at reflux for 15 hours. After cooling the solid was filtered, and the filtrate was concentrated, washed with ethyl ether. The washing was concentrated further to a solid. Additional washing with cold ethyl ether (10 mL) afforded *N*-(4-chlorophenyl)-2-aminobenzamide as a tan solid; NMR (DMSO-d_6) 10.1 (s, 1), 7.8 (d, 2), 7.6 (d, 1), 7.4 (d, 2), 7.2 (t, 1), 6.8 (d, 1), 6.6 (t, 1), 6.3 (s, 2) ppm.

B. In a similar manner, the following compounds were made:
N-(4-chlorophenyl)-2-amino-4,5-difluorobenzamide; NMR (DMSO-d_6) 10.1 (s, 1), 7.8 (m, 3), 7.4 (d, 2), 6.7 (dd, 1), 6.6 (br s, 2) ppm;
N-(4-chlorophenyl)-2-amino-5-fluorobenzamide;
N-(4-chlorophenyl)-2-amino-4-fluorobenzamide;
N-(4-chlorophenyl)-2-amino-3-methylbenzamide; and
N-(4-chlorophenyl)-3-aminopyridin-4-amide.

C. In a similar manner, other compounds of formula (Ec) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 15

Compound of Formula (OO)

A. To 2-methoxycarbonyl-3-chloro-4-(chloromethyl)thiophene (48 g, 0.21 mol) in glacial acetic acid (500 mL) was added sodium acetate (35 g, 0.42 mol). The reaction was heated at reflux for 24 hours, then cooled and concentrated *in vacuo*. The residual oil was made basic by addition of saturated aqueous sodium bicarbonate, and the resulting solution extracted with ethyl acetate (4x150 mL). The combined extracts were dried over sodium sulfate and concentrated to afford 47 g (90% yield) of 2-methoxycarbonyl-3-chloro-4-(acetoxymethyl)thiophene as a light brown oil; NMR ($CDCl_3$) 7.6 (s, 1), 5.1 (s, 2), 3.9 (s, 3), 2.1 (s, 3) ppm.

B. In a similar manner, other compounds of formula (OO) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 16

Compounds of Formula (PP)

A. To a solution of 2-methoxycarbonyl-3-chloro-4-(acetoxymethyl)thiophene (83 g, 0.33 mol) in 1,4-dioxane (350 mL) was added a solution of sodium hydroxide (26.5 g, 0.66 mol) in water (200 mL) and the mixture stirred at ambient temperature. After 1 hour the dioxane was removed *in vacuo* and the aqueous solution washed with ethyl acetate (2x100 mL). The aqueous layer was brought to pH 2 by addition of concentrated HCl, then extracted with *n*-butanol (4x200 mL). The combined extracts were concentrated and the resulting solid dried *in vacuo* to afford 63 g (90% yield) of 2-carboxy-3-chloro-4-(hydroxymethyl)thiophene as a tan powder; NMR (DMSO-d_6) 7.7 (s, 1), 4.4 (s, 2) ppm.

B. In a similar manner, the following compound was prepared:
2-carboxy-3-chloro-4-(2-(*N*-methyl-*N*-*tert*-butoxycarbonylamino)ethyl)thiophene.

C. In a manner similar to that described above in Paragraph A, 2-methoxycarbonyl-3-chloro-4-((morpholin-4-yl)methyl)thiophene (2.0 g, 8.2 mmol) was reacted with aqueous sodium hydroxide (1 M, 8.2 mL, 8.2 mmol) in 1,4-dioxane (20 mL). Concentration of all volatiles *in vacuo* afforded 2.0 g (86% yield) of the sodium salt of 2-carboxy-3-chloro-4-((morpholin-4-yl)methyl)thiophene; NMR (DMSO-d_6) 7.3 (s, 1), 3.5 (m, 4), 3.3 (d, 2), 2.3 (m, 4) ppm.

D. In a similar manner, the following compound was made:

2-carboxy-3-chloro-4-((thiomorpholin-4-yl)methyl)thiophene sodium salt.

E. In a manner similar to that described above, other compounds of formula (PP) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 17

Compounds of Formula (F)

A. 2-carboxy-3-chloro-4-(hydroxymethyl)thiophene (83 g, 0.43 mmol) was added to thionyl chloride (200 mL) and the mixture heated at reflux for 4-6 hours. After cooling to ambient temperature, the mixture was concentrated of all volatiles *in vacuo* followed by repeated concentration from 1,2-dichloroethane. The residual oil was dissolved in methylene chloride (250 mL), filtered and concentrated to afford 100 g (89% yield) of 2-chlorocarbonyl-3-chloro-4-(chloromethyl)thiophene as a tan waxy solid; NMR ($CDCl_3$) 7.8 (s, 1), 4.6 (s, 2) ppm.

B. In a similar manner, other compounds of formula (F) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 18

Compounds of Formula (RR)

A. To 5-carboxy-1,3-benzodioxole (50 g, 300 mmol) in trifluoroacetic acid (400 mL) at 0°C was added HNO_3 (38 mL, 900 mmol) dropwise. The reaction mixture was stirred at 0°C for 1 hour, then warmed to ambient temperature and stirred for 3 hours. The mixture was poured into ice water and the resulting precipitate was collected by filtration. The solid was air dried overnight to afford 58 g (92% yield) of 5-carboxy-6-nitro-1,3-benzodioxole as a yellow solid; NMR (DMSO-d_6) 7.6 (s, 1), 7.3 (s, 1), 6.3 (s, 2) ppm.

B. In a similar manner, other compounds of formula (RR) and corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 19

A. To a suspension of 2-carboxy-3-chloro-5-methylthiophene (1.2 g, 6.6 mmol) in methylene chloride (16 mL) at 0°C were added oxalyl chloride (0.6 mL, 7.3 mmol) and a drop of DMF. The mixture was stirred at ambient temperature for 5 hours, then concentrated of all volatiles and dried *in vacuo* to afford 1.3 g (quantitative yield) of 2-chlorocarbonyl-3-chloro-5-methylthiophene as a pale yellow solid; NMR (DMSO-d_6/TFA) 7.4 (s, 1), 2.5 (s, 3) ppm.

B. In a similar manner, the following compounds were made:

2-chlorocarbonyl-3-methoxybenzo[*b*]thiophene;

2-chlorocarbonyl-3-chloro-4-cyanothiophene;

2-chlorocarbonyl-3-methyl-5-nitrothiophene;

2-chlorocarbonyl)-3-methyl-4-nitrothiophene; and

2-chlorocarbonyl-3-chloro-4-(2-(*N*-methyl-*N*-*tert*-butoxycarbonylamino)ethyl)thiophene.

C. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 20

A. To a solution of 3,5-dichlorobenzoic acid (50 g, 0.26 mol) in sulfuric acid (250 mL) at 0°C was added nitric acid (18 g, 0.28 mol) dropwise, and the mixture warmed slowly to ambient temperature. After 5 hours the mixture was poured onto ice, and the white precipitate collected by filtration. The solid was washed with water (3x30 mL), and dried *in vacuo* to afford 55 g (90% yield) of 3,5-dichloro-2-nitrobenzoic acid; NMR ($CDCl_3$) 8.3 (s, 1), 8.0 (s, 1) ppm.

B. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 21

A. To a solution of (*R*)-(-)-1-amino-2-propanol (0.40 g, 5.3 mmol) in methanol (10 mL) at 0°C were added sodium acetate (0.82 g, 10 mmol) and cyanogen bromide (5 M in acetonitrile, 1 mL, 5.0 mmol). The reaction was allowed to warm slowly to ambient temperature and stirred for 2 hours. The mixture was concentrated *in vacuo*. A small amount of water was added and the solution made basic by addition of a saturated aqueous K_2CO_3 solution. The mixture was extracted with methylene chloride, dried over K_2CO_3, and concentrated *in vacuo* to afford 0.3 g (60% yield) of 2-imino-5(*R*)-methyloxazolidine; NMR (DMSO-d_6/TFA) 5.7 (br s, 2), 4.5 (m, 1), 3.6 (dd, 1). 3.0 (dd, 1), 1.2 (d, 3) ppm.

B. In a similar manner, the following compounds were made:

2-imino-5(*S*)-methyloxazolidine; NMR (DMSO-d_6/TFA) 5.7 (br s, 2), 4.5 (m, 1), 3.6 (dd, 1). 3.0 (dd, 1), 1.2 (d, 3) ppm;

2-imino-5-methyloxazolidine; NMR (DMSO-d_6/TFA) 5.7 (br s, 2), 4.5 (m, 1), 3.6 (dd, 1), 3.0 (dd, 1), 1.2 (d, 3) ppm;

2-imino-5,5-dimethyloxazolidine; NMR (DMSO-d_6/TFA) 3.3 (s, 2), 1.3 (s, 6) ppm; and

2-imino-4-methyloxazolidine.

C. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 22

A. To a solution of 1-amino-2-methyl-2-propanol (4.0 g, 45 mmol) in CH_2Cl_2 (25 mL) at 0°C was added a solution of ethyl isocyanate (3.2 g, 45 mmol) in CH_2Cl_2 (5 mL) dropwise. The mixture was stirred at ambient temperature for 18 hours, then concentrated of all volatiles *in vacuo* to afford a quantitative yield of *N*-(2-methyl-2-hydroxypropyl)-*N'*-ethylurea as a yellow solid; NMR (DMSO-d_6/TFA) 5.9 (m. 1), 5.7 (m, 1), 3.0 (m, 2), 2.9 (d, 2), 1.0 (s, 6), 0.9 (t, 3) ppm.

B. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 23

A. To a solution of *N*-(2-methyl-2-hydroxypropyl)-*N'*-ethylurea (7.2 g, 45 mmol) in CH_2Cl_2 (100 mL) at 0°C was added a solution of thionyl chloride (5.4 g, 45 mmol) in CH_2Cl_2 (20 mL). The mixture was warmed to ambient temperature. After 2 hours, the mixture was concentrated *in vacuo*, and the resulting solid triturated with boiling water. The mixture was cooled to ambient temperature and made basic by addition of saturated aqueous K_2CO_3. The mixture was extracted with methylene chloride, dried over K_2CO_3, and concentrated *in vacuo* to afford 3.2 g (50% yield) of 2-ethylamino-5,5-dimethyloxazoline; NMR (DMSO-d_6/TFA) 3.2 (s, 2), 3.0 (q, 2), 1.3 (s, 6), 1.0 (t, 3) ppm.

B. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 24

A. To a solution of 1-amino-2-propanol (2.0 g, 27 mmol) in tetrahydrofuran (20 mL) was added a solution of thiocarbonyldiimidazole (5.3 g, 27 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at ambient temperature for 3 hours, then concentrated *in vacuo*. Purification by flash chromatography on silica gel afforded 2.9 g (93% yield) of 5-methyl-2-thioxooxazolidine; NMR ($CDCl_3$) 8.4 (br s, 1), 5.0 (m, 1), 3.8 (t, 1). 3.4 (t, 1), 1.5 (d, 3) ppm;

B. In a similar manner, the following compound was made:
4-methyl-2-thioxooxazolidine.

C. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 25

A. To a solution of 5-methyl-2-thioxooxazolidine (2.7 g, 23 mmol) in $POCl_3$ (40 mL) was added PCl_5 (4.8 g, 23 mmol). The mixture was heated at 100°C for 3 hours, then cooled to ambient temperature and concentrated *in vacuo*. The resulting yellow oil was dissolved in methylene chloride, filtered through silica gel and concentrated to afford a quantitative yield of 2-chloro-5-methyl-2-oxazoline.

B. In a similar manner, the following compound was made: 2-chloro-4-methyl-2-oxazoline.

C. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 26

A. To a solution of 2-carboxy-3-chlorothiophene (2.0 g, 12.3 mmol) in chloromethyl methyl ether (10 mL) was added $TiCl_4$ (4.0 mL, 6.9g, 36 mmol) at 0°C under N_2. The resulting dark orange suspension was warmed to ambient temperature. After 5 hours the reaction mixture was poured onto methylene chloride (75 mL) and ice water (100 mL) with vigorous stirring. The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL) and the combined organics extracted with 3 portions of aqueous $NaHCO_3$ (100 mL, 25-50% saturated). The combined aqueous extracts were made acidic by addition of concentrated HCl and the resulting precipitate extracted into ethyl acetate (3x100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated of all volatiles *in vacuo*. The resulting solid was dissolved in acetonitrile, water and trifluoroacetic acid and purified by HPLC on a C18 Dynamax column with 30-55% acetonitrile in water gradient with 0.1% trifluoroacetic acid to afford 0.83 g (26% yield) of 2-carboxy-3-chloro-4,5-di(chloromethyl)thiophene as a white solid: NMR ($CDCl_3$) 4.8 (s, 2), 4.6 (s, 2) ppm.

B. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 27

A. *N*-(5-Chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.054 g, 0.11mmol) and 1,1-di(methylthio)-2-nitroethene (0.092 g, 0.56mmol) were dissolved in DMF (1 mL) and stirred at 50°C under nitrogen for 16 hours. The reaction mixture was then partitioned between water (25 mL) and ethyl acetate (60 mL), the layers were separated and the aqueous layer extracted with ethyl

acetate (30 mL). The combined organic layers were washed with water (3x30 mL), brine (30 mL), dried over magnesium sulfate, concentrated *in vacuo*, and dried under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with 70% ethyl acetate/hexanes to give *N*-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-nitro-1-methylthioethenyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide as a yellow foam.

B. In a similar manner, the following compound was made: *N*-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(methylthio(cyanoimino)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

C. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 28

A. *N*-(5-Chloropyridin-2-yl)-2-[((4-(2-amino-2-(hydroxyimino)ethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (3.06 g, 5.8mmol) was dissolved in trichloroacetic acid (3.8 g, 23 mmol) and the mixture heated to 85°C. Trichloroacetyl chloride (1.3 mL, 11.6 mmol) was added, and the temperature was increased to 94°C. After one hour the reaction mixture was allowed to cool to room temperature, diluted with water (150 mL) and a small amount of ethyl acetate, and adjusted to basic pH with 1 N NaOH. The aqueous layer was extracted with ethyl acetate (300 mL). The organic phase was washed with 1 M sodium bicarbonate (150 mL), dried over magnesium sulfate, concentrated *in vacuo*, and dried under vacuum. The crude product was purified by flash chromatography on silica gel eluting with 25% ethyl acetate/hexanes to afford *N*-(5-chloropyridin-2-yl)-2-[((4-((5-trichloromethyl-1,2,4-oxadiazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

B. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 29

A. To a solution of 2-carboxy-3-methylthiophene (10 g, 70.3 mmol) in 80 mL of trifluoroacetic acid at 0°C was added HNO_3 (1.2 mL,1.0 eq.) dropwise. The reaction mixture was warmed to ambient temperature and after 4 hours another 1.0 eq. of HNO_3 was added. The reaction mixture was made basic with aqueous sodium bicarbonate and washed with ethyl acetate. The aqueous layer was acidified with concentrated HCl and extracted with ethyl

acetate. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford 5.75 g (53%) of 2-carboxy-3-methyl-5-nitrothiophene and 2-carboxy-3-methyl-4-nitrothiophene, as a yellow solid.

B. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 30

A. *N-tert*-Butoxycarbonylpiperazine (2.94 g, 16.0 mmol) was dissolved in pyridine (8 mL) under nitrogen and the solution cooled to 0°C. Methanesulfonyl chloride (1.5 mL, 19.3 mmol) was added. After 5 minutes, more pyridine was added (5 mL) and the reaction mixture was allowed to warm to ambient temperature. After 40 minutes, the pyridine was removed *in vacuo*. The residue was dissolved in ethyl acetate (250 mL), washed with 0.1M citric acid (3x125 mL), dried over magnesium sulfate, concentrated *in vacuo*, and dried under vacuum to give 3.84 g (92%) of *N-tert*-butoxycarbonyl-*N'*-methylsulfonylpiperazine.

B. *N-tert*-butoxycarbonyl-*N'*-methylsulfonylpiperazine (3.84 g, 14.5 mmol) was suspended in methylene chloride (100 mL) under nitrogen and trifluoroacetic acid (10mL) was added. After 3 hours, the reaction mixture was concentrated *in vacuo* and the residue dissolved in water (150 mL). The aqueous layer was washed with ether (2x75 mL). The pH of the aqueous layer was then adjusted to 10 and it was extracted with methylene chloride (3x120mL). The methylene chloride layers were dried over magnesium sulfate, and concentrated *in vacuo* to give 0.99 g of *N*-methylsulfonylpiperazine. Further extraction of the aqueous layer with 10% methanol/methylene chloride (3x120 mL) afforded 0.44 g of *N*-methylsulfonylpiperazine, for a total of 1.43 g (59%).

C. In a similar manner, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 31

A. Hydroxylamine hydrochloride (6.12 g, 88 mmol) was added to a solution of sodium methoxide prepared by dissolving sodium (2.02 g) in methanol (25 mL). Additional methanol (50 mL) was added, followed by (methylthio)acetonitrile (6.0 mL, 71.5 mmol). The reaction mixture was refluxed for 5 hours, filtered while hot, concentrated *in vacuo*, and dried under vacuum to give 1-amino-1-hydroxyimino-2-methylthioethane in quantitative yield.

B. In a similar manner, 1-amino-1-hydroxyimino-2-methoxyethane was prepared.

C. 1-Amino-1-hydroxyimino-2-methylthioethane (11.32 g, 94.2 mmol) was suspended in dry chloroform (60 mL) under nitrogen. A solution of chloroacetyl chloride (7.5 mL, 94.2 mmol) in chloroform (20 mL) was added dropwise. After stirring for 1 hour, a solution of triethylamine (15.8 mL, 113 mmol) in chloroform (20 mL) was added dropwise. The reaction mixture was stirred for 15 minutes, then washed with water (2x70 mL), dried over sodium sulfate, concentrated *in vacuo*, and dried under vacuum to yield 11.4 g (62% yield) of 1-amino-1-((chloromethyl)carbonyloxy)imino-2-methylthioethane, as a brown semi-solid.

D. In a similar manner, 1-amino-1-((chloromethyl)carbonyloxy)imino-2-methoxyethane was prepared.

E. 1-Amino-1-((chloromethyl)carbonyloxy)imino-2-methylthioethane (3.04 g, 15.5 mmol) was dissolved in xylenes (15 mL) under nitrogen. The reaction mixture was refluxed for 3 hours, concentrated *in vacuo*, and dried under vacuum. The crude product was purified by flash chromatography on silica eluting with 10% ethyl acetate/hexanes to give 1.14 g (41% yield) of 5-chloromethyl-3-methylthiomethyl-1,2,4-oxadiazole.

F. In a similar manner, 5-chloromethyl-3-methylthiomethyl-1,2,4-oxadiazole was prepared.

G. In a manner similar to those methods described above, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 32

A. Acetic anhydride (30.91 g, 0.303 mol) was cooled to 0°C and formic acid (20.6 g, 0.394 mol) was added dropwise. After stirring for 30 minutes at 0°C, the reaction mixture was warmed to room temperature then heated to 50°C. The reaction mixture was stirred for 5 hours, then cooled to ambient temperature. The product, acetic formic anhydride, was used in the next step without further purification.

B. To a solution of acetic formic anhydride (26.7 g, 0.303 mol) in THF (100 mL) was added 2-aminoimidazole (25. 2 g, 0.303 mol) in THF (200 mL) at ambient temperature. After stirring for 16 hours, the reaction mixture was concentrated and the resulting solid was suspended in methylene chloride. NH_3 (g) was bubbled into the suspension and the reaction mixture was concentrated. The resulting white slurry was loaded onto a silica column and eluted with 0-10% methanol in methylene chloride gradient to afford 25.9 g of 2-(formylamino)imidazole as a white solid.

C. In a similar manner the following compound was prepared: 2-(acetylamino)imidazole.

D. To a suspension of 2-(formylamino)imidazole (25.9 g, 0.233 mol) in THF (200 mL) was added BH_3-THF (900 mL of a 1 M solution in THF, 0.9 mol) at ambient temperature. The resulting white turbid solution was stirred at ambient temperature for 16 hours. The reaction was quenched with methanol and adjusted to pH 2 with 3 N HCl in ethyl acetate. The solution was heated to reflux for an hour and then was concentrated. The resulting solid was dissolved in THF and NH_3 (g) was bubbled into the solution. The resulting white solid was removed by filtration and the filtrate was concentrated to afford 2-(methylamino)imidazole as a dark oil.

E. In a similar manner the following compound was prepared: 2-(ethylamino)imidazole.

F. In a manner similar to those methods described above, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 33

A. To a solution of 2-methoxycarbonyl-3-chloro-4-hydroxymethylthiophene (6 g, 29 mmol) in methylene chloride (100 mL) were added triethylamine (8.1 mL, 58 mmol) and methanesulfonyl chloride (2.5 mL, 32 mmol) at ambient temperature. After stirring for 6 hours, the reaction mixture was concentrated to afford 2-methoxycarbonyl-3-chloro-4-(methylsulfonyloxy)methylthiophene. The crude product was dissolved in DMF (150 mL) and excess potassium cyanide was added to the solution. The reaction mixture was stirred at ambient temperature for 16 hours, then poured into water, and extracted with methylene chloride. The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 2-methoxycarbonyl-3-chloro-4-cyanomethylthiophene.

B. 2-Methoxycarbonyl-3-chloro-4-cyanomethylthiophene (2 g, 9.27 mmol) was dissolved in THF (100 mL) and BH_3-THF (18.6 mL of a 1 M solution in THF, 18.6 mmol) was added. After stirring for 16 hours at ambient temperature, the reaction was quenched with water followed by 1 M NaOH. Potassium carbonate was added to afford two layers. The organic layer was separated and concentrated *in vacuo* to afford 2-methoxycarbonyl-3-chloro-4-(2-aminoethyl)thiophene.

C. 2-Methoxycarbonyl-3-chloro-4-(2-aminoethyl)thiophene was dissolved in THF (50 mL), and di-*tert*-butyl dicarbonate (2.23 g, 10.2 mmol) was added at ambient temperature. After 1 hour, water was added, and the reaction mixture was extracted with methylene chloride. The combined extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash chromatography on gel to afford 1.42 g of 2-methoxycarbonyl-3-chloro-4-(2-(*tert*-butoxycarbonylamino)-ethyl)thiophene.

D. To a solution of 2-methoxycarbonyl-3-chloro-4-(2-(*N*-methyl-*N*-*tert*-butoxycarbonylamino)ethyl)-thiophene (0.93 g, 2.91 mmol) in DMF (10 mL) were added NaH (0.23 g, 5.82 mmol) and iodomethane (0.36 mL, 5.82 mmol) at ambient temperature. After stirring for 48 hours, water was added, and the reaction mixture was extracted with methylene chloride. The combined extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash chromatography on silica to afford 2-methoxycarbonyl-3-chloro-4-(2-(*N*-methyl-*N*-*tert*-butoxycarbonylamino)ethyl)thiophene (0.45 g).

E. In a manner similar to those methods described above, other corresponding intermediates of the compounds of the invention may be prepared.

PREPARATION 34

A. To a solution of 2-chloro-3-nitropyridine (5 g, 31.6 mmol, 1.0 eq.) in 50 mL of DMF was added copper cyanide (2.47 g, 38 mmol, 1.2 eq.) and the reaction heated to 100°C for 16 hours. The reaction mixture was cooled to ambient temperature and poured into 100 mL of water. The mixture was extracted with ethyl acetate (3x50 mL) and the combined ethyl acetate portions were dried over soduim sulfate and concentrated. The crude material was chromatographed on silica with 3:7 ethyl acetate/hexanes to give 2-cyano-3-nitropyridine as a yellow solid.

B. To a solution of 2-cyano-3-nitropyridine (0.5 g, 3.4 mmol, 1 eq.) in 50 mL of ethanol was added HCl gas. The reaction was stirred at ambient temperature for 16 hours and concentrated. The residue was dissolved in 50 mL of water and the solution neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl actetate (3x50 mL). The combined ethyl acetate extractions were dried over sodium sulfate and concentrated. The residue was chromatographed to give 2-ethoxycarbonyl-3-nitropyridine (0.5 g, 90% yield) as a pale yellow oil.

C. To a solution of 2-ethoxycarbonyl-3-nitropyridine (0.5 g, 2.5 mmoL, 1 eq.) in 20 mL of methanol and 5 mL of water was added lithium hydroxide (0.2 g, 4.5 mmoL, 1.8 eq.) and the mixture stirred for 16 hours at ambient temperature. The reaction was concentrated and 50 mL of 1N KOH was were added. The solution was washed with 25 mL of ethyl acetate, acidified with 1 N HCl, and extracted with ethyl acetate (3x50 mL). The combined ethyl acetate extractions were dried over sodium sulfate and concentrated to give 2-carboxy-3-nitropyridine as a yellow solid (0.4 g, 95% yield).

D. In a manner similar to those methods described above, other intermediates for compounds of the invention where the B ring is a heterocyclic may be prepared.

EXAMPLE 1

Compounds of Formula (Ia)

A. To a solution of *N*-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (1.0 g, 2.1 mmol) in DMF (40 mL) at 0°C was added 1-methylpiperazine (1.2 mL, 1.1 g, 11 mmol), and the mixture stirred for 0.5 hours at 0°C, then warmed to ambient temperature. After 7 hours the reaction mixture was poured into water (150 mL) and the resulting solid collected by filtration, washed with water (50 mL) and acetonitrile (10 mL). Purification by flash chromatography on silica gel afforded 0.77 g (64% yield) of *N*-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, as a white foam: NMR (DMSO-d_6/TFA) 10.4 (s, 1), 9.4 (s, 1), 7.2-8.1 (m, 7), 4.4 (s, 2), 3.8 (s, 3), 3.0-3.8 (br m, 8), 2.8 (s, 3) ppm.

B. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.7 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (s, 1), 7.8 (dd, 1), 7.7 (d, 1), 7.5 (d, 1), 4.4 (s, 2), 3.6-3.3 (br m, 8), 2.9 (s, 6), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(3-(dimethylamino)propyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.7 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.6 (d, 1), 7.5 (d, 1), 4.4-4.3 (br m, 2), 3.2-3.0 (br m, 4), 2.9 (s, 6), 2.8 (d, 6), 2.7 (s, 3), 2.3 (br s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.7 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.6 (d, 1), 7.4 (d, 1), 4.4 (br s, 2), 3.5 (br s, 4), 2.9 (s, 12), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(dimethyl)amino-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.7 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.7 (d, 1), 7.5 (d, 1), 4.5-4.3 (br m, 2), 3.65-3.5 (br m, 3), 3.1-3.0 (br m, 2), 2.9 (s, 6), 2.8 (s, 3), 2.7 (s, 3), 2.4-2.3 (br m, 2), 2.1-1.9 (br m, 2) ppm;

N-(pyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 8.5 (d, 1), 8.3 (t, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (s, 1), 7.8 (d, 1), 7.6 (d, 1), 7.5 (t, 1), 4.4 (s, 2), 3.6-3.2 (br m, 8), 2.9 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(3-(imidazol-1-yl)propyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 9.1 (s, 1), 8.4 (d, 1), 8.2 (s, 1), 7.9 (d, 1), 7.8-7.6 (m, 5), 7.4 (d, 2), 4.3 (t, 2), 4.2 (br s, 2), 3.0 (br s, 2), 2.2 (m, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(2-(morpholin-4-yl)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 7.4-8.5 (m, 7), 3.3-3.7 (m, 8), 2.4-2.7 (m, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(2-(morpholin-4-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 7.4-8.6 (m, 7), 3.6 (s, 2), , 3.0-3.7 (m, 8), 2.2-2.7 (m, 6) ppm; /TFA)

N-(5-chloropyridin-2-yl)-2-[((4-((4-hydroxypiperidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 9.4 (s, 1), 8.3 (s, 1), 8.2 (d, 1), 8.1 (s, 1), 7.8 (d, 1), 7.4 (s, 1), 7.3 (s, 1), 4.3 (m, 2), 3.9 (s, 3), 3.8 (br s, 1), 3.4 (m, 1), 3.2 (m, 2), 3.0 (m, 1), 1.8 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 10.1 (br s, 1), 8.4 (d, 1), 8.3 (s, 1), 7.9 (s, 1), 7.7 (d, 2), 7.6 (d, 1), 7.4 (d, 2), 4.4 (s, 2), 3.6 (m, 2), 3.4 (br s, 6), 2.8 (s, 3), 2.0 (br s, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (br s, 1), 9.4 (s, 1), 8.3 (s, 1), 8.2 (m, 1), 8.1 (d, 1), 7.9 (d, 1), 7.4 (s, 1), 7.3 (s, 1), 4.4 (m, 2), 4.0 (m, 1), 3.9 (s, 3), 3.4 (m, 2), 3.1 (m, 2), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-ethyl-*N'*-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 9.4 (br s, 1), 8.4 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (d, 1), 7.4 (s, 1), 7.3 (s, 1), 4.4 (br s, 2), 3.9 (s, 3), 3.8 (m, 2), 3.2 (m, 4), 1.3 (m, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.2 (s,1), 10.8 (s,1), 10.0 (br s,1), 8.4 (d,1), 8.3 (s,1), 8.0 (s,1), 7.8 (d,2), 7.7 (d,1), 7.4 (d,2), 4.4 (s,2), 3.6 (m,4), 3.3 (br s,2), 2.8 (s,3), 2.0 (br s, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(pyrrolidin-1-yl)-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (s, 1), 8.2 (d, 1), 8.1 (s, 1), 7.9 (d, 1), 7.0 (s, 1), 6.9 (s, 1) 4.3 (s, 2), 3.5 (br s, 4), 3.4 (br s, 8), 2.9 (s, 3), 1.9 (br s, 4) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR ($CDCl_3$) 11.1 (s, 1), 8.7 (s, 1), 8.3 (d, 1), 7.7 (d, 2), 7.5 (s, 2), 7.4 (d, 2), 7.3 (dd, 1), 3.7 (t, 2), 3.6 (s, 2), 2.7 (t, 2), 2.3 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.1 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 7.9 (s, 1), 7.8 (s, 1), 7.7 (d, 2), 7.6 (d, 1), 7.4 (d, 2), 3.4 (s, 2), 2.4 (m, 4), 2.3 (m, 4), 2.1 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-methyl-*N*'-(2-dimethylaminoethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.1 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 7.9 (d, 1), 7.8 (s, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.4 (d, 2), 3.5 (s, 2), 2.5 (d, 2), 2.3 (d, 2), 2.2 (s, 3), 2.1 (s, 6) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-methyl-*N*'-(ethoxycarbonylmethyl)amino)methyl)-thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR ($CDCl_3$) 11.1 (s, 1), 8.6 (s, 1), 8.3 (d, 1), 7.7 (d, 2), 7.6 (s, 1), 7.5 (d, 1), 7.4 (d, 2), 7.3 (dd, 1), 4.2 (q, 2), 3.7 (s, 2), 3.3 (s, 2), 2.5 (s, 3), 1.3 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(3-(dimethylamino)propyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 8.3 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.7 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 3.9 (s, 3), 3.4 (s, 2), 2.4 (t, 2), 2.2 (t, 2), 2.1 (s, 3), 2.0 (s, 6), 1.5 (m, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.3 (s, 1), 8.4 (s, 1), 8.1 (d, 1), 7.9 (d, 1), 7.7 (s, 1), 7.4 (s, 1), 7.2 (s, 1), 3.9 (s, 3), 3.4 (s, 2), 3.3 (s, 3), 2.2-2.5 (br m, 11), 1.0 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.9 (s, 1), 9.4 (s, 1), 8.4 (s, 1), 8.1 (d, 1), 7.9 (d, 1), 7.8 (s, 1), 7.4 (s, 1), 7.2 (s, 1), 4.4 (t, 1), 3.9 (s, 3), 3.5 (m, 4), 3.3 (d, 2), 2.4 (m, 3) ppm;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole, NMR (DMSO-d_6/TFA) 11.5 (s, 1), 11.0 (s, 1), 9.6 (s, 1), 7.5-8.4 (m, 6), 6.1 (s, 2), 4.4 (m, 2), 3.8 (t, 2), 3.2 (m, 2), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (br s, 1), 9.3 (br s, 1), 8.3 (s, 1), 8.1 (d, 1), 7.9 (d, 1), 7.8 (s, 1), 7.2 (s, 1), 7.1 (s,

1), 3.6 (m, 1), 3.5 (br s, 2), 3.3 (m, 2), 2.5 (m, 1), 2.3 (m, 1), 2.2 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((*t*-butyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (br, 1), 9.4 (br, 1), 8.3 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.7 (s, 1), 7.4 (s, 1), 7.2 (s, 1), 3.9 (s, 3), 3.6 (s, 2), 1.1 (s, 9) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-(2-hydroxyethoxy)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((4-hydroxycyclohexyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-(((2-methoxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-methoxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.8 (s, 1), 9.5 (br s, 1), 9.4 (s, 1), 8.2 (d, 1), 8.1 (s, 1), 8.0 (d, 1), 7.8 (dd, 1), 7.1 (s, 2), 4.3 (br d, 2), 3.75 (t, 2), 3.15 (br m, 4), 1.2 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3,4,5-trimethoxybenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(ethylamino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.90 (s, 1H), 9.40 (s, 1H), 8.80 (br s, 2H), 8.75 (d, 1H), 8.20 (d, 1H), 8.10 (s, 1H), 7.80 (dd, 1H), 7.48 (d, 1H), 7.60 (d, 1H), 4.15 (s, 2H), 3.85 (s, 3H), 3.05 (br s, 2H), 1.20 (t, 3H) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.90 (s, 1H), 9.38 (s, 1H), 8.30 (d, 1H), 8.20 (d, 1H), 7.90 (dd, 1H), 7.70 (s, 1H), 7.40 (d, 1H), 7.25 (d, 1H), 3.90 (s, 3H), 3.30 (s, 2H), 2.40 (q, 2H), 2.10 (s, 3H), 1.00 (t, 3H) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-formylpiperazin-1-yl)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 3.9 (s, 3), 3.5 (s, 2), 3.3 (s, 4), 2.4 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((pyrrolidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCl_3$) 9.1 (s, 1), 8.8 (s, 1), 8.3 (d, 1), 8.2 (d, 1), 7.7 (dd, 1), 7.5 (s, 1), 7.3 (d, 1), 7.1 (d, 1) 3.9 (s, 3), 3.6 (s, 2), 2.6 (m, 4), 1.8 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(1-methylethyl)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 12.4 (s, 1), 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (d, 2), 7.6 (s, 1), 7.3 (dd, 2), 7.0 (br d, 2), 5.1 (s, 2), 3.9 (s, 3), 3.8 (m, 1), 1.2 (d, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((morpholin-4-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCL_3$) 9.1 (s, 1), 8.7 (s, 1), 8.2 (d, 1), 8.1 (s, 1), 7.6 (dd, 1), 7.4 (s, 1), 7.2 (d, 1), 7.0 (s, 1), 3.9 (s, 3), 3.7 (bs, 4), 3.5 (s, 2), 2.5 (bs, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(1-methylethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCL_3$) 9.1 (s, 1), 8.9 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 7.6 (dd, 1), 7.4 (s, 1), 7.3 (s, 1), 7.05 (s, 1), 3.9 (s, 3), 3.8 (s, 2), 2.9 (m, 1), 1.0 (d, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(diethylamino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 9.4 (s, 1), 8.4 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (d, 1), 7.3 (s, 1), 7.2 (s, 1), 4.2 (s, 2), 3.8 (s, 3), 3.1 (bs, 4), 1.2 (m, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-4-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (br s, 1), 9.4 (s, 1), 9.2 (br s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.2 (d, 2), 4.8 (t, 1), 4.6 (dd, 2), 4.3 (t, 1), 4.1 (m, 1), 3.8 (s, 3), 1.2 (d, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 3.9 (s, 3), 3.5 (s, 2), 3.1 (s, 4), 2.9 (s, 3), 2.5 (s, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((2(*S*),3(*S*)-3-hydroxybut-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((2(*R*),3(*S*)-3-hydroxybut-2-yl)amino)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((aminocarbonylmethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-(((3-aminopropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(*N*"-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(pyrrolin-1-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((di(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide.

C. In a manner similar to Paragraph A above, *N*-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide(2.0 g, 4.0 mmol) was reacted with 2-aminoimidazole (1.3 g, 16 mmol) to give *N*-(5-chloropyridin-2-yl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, which was purified by HPLC on a C18 Vydac column with acetonitrile in water gradient with 0.1% trifluoroacetic acid to afford *N*-(5-chloropyridin-2-yl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt, as a white solid; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 10.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (br, 1), 7.6 (s, 1), 4 (d, 1), 7.3 (d, 1), 6.9 (dt, 1), 5.0 (s, 2), 4.8 (s, 3) ppm.

D. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5(*S*)-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, , trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.4 (s, 1), 7.3 (s, 1), 5.1 (m, 1), 4.6 (q, 2), 3.9 (s, 3), 3.9 (d, 1), 3.4 (t, 1), 1.4 (d, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((thiazol-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; , trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.7 (s, 1), 7.4 (d, 1), 7.4 (d, 1), 7.3 (d, 1), 7.1 (d, 1), 5.2 (s, 2), 3.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.5 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.5 (d, 2), 3.6 (s, 2), 3.5 (br m, 2), 3.4 (br m, 4), 3.2-2.8 (br m, 8), 2.8 (s, 3), 2.7

(s, 3), 2.6-2.4 (br m, 2) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-methyl-*N*'-(2-diethylaminoethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.3 (m, 2), 8.0 (s, 1), 7.7 (m, 3), 7.4 (d, 2), 4.4 (s, 2), 3.5 (m, 3), 3.2 (q, 4), 2.8 (s, 3), 1.2 (t, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.6 (s, 1), 8.4 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.4 (d, 2), 4.4 (br d, 2), 3.8 (t, 2), 3.5 (m, 2), 3.3 (m, 2), 3.2 (m, 2), 3.1 (d, 4), 2.8 (s, 3), 2.7 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.4 (s, 1), 7.3 (s, 1), 5.1 (m, 1), 4.6 (q, 2), 3.9 (s, 3), 3.9 (d, 1), 3.4 (t, 1), 1.4 (d, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5,5-(dimethyl)tetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.4 (s, 1), 7.3 (s, 1), 4.6 (s, 2), 3.8 (s, 3), 3.5 (s, 2), 1.5 (s, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-ethylimino-5,5-(dimethyl)tetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 7.9 (s, 1), 7.8 (dd, 1), 7.3 (s, 1), 7.2 (s, 1), 4.6 (s, 2), 3.8 (s, 3), 3.5 (s, 2), 3.3 (q, 2), 1.4 (s, 6), 1.1 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-5(*R*)-methyltetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.4 (s, 1), 7.3 (s, 1), 5.1 (m, 1), 4.6 (q, 2), 3.9 (s, 3), 3.9 (d, 1), 3.4 (t, 1), 1.4 (d, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 3.9 (s, 2), 3.7 (br d, 4), 3.0-3.7 (m, 8), 2.9 (br d, 2), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide,

trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.4 (m, 6), 4.1 (br d, 2), 2.6-3.8 (m, 14) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 4.1 (br d, 2), 2.8-3.8 (m, 14) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)-3-chlorothiophen-2-yl)carbonyl)amino]-3-chloro-5-(*N*'-methyl-*N*'-(ethoxycarbonyl)methylamino)benzamide; trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 6.9-8.4 (m, 6), 5.6 (s, 2), 4.4 (s, 2), 4.3 (s, 2), 4.1 (q, 2), 3.5 (br d, 4), 3.0 (s, 3), 2.8 (s, 3), 2.7 (s, 3), 1.2 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 4.2 -4.5 (m, 2), 3.6-3.9 (m, 6), 3.1-3.3 (m, 2), 2.9 (br d, 2), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 7.3-8.5 (m, 6), 3.0-4.2 (m, 14), 2.9 (s, 3), 2.5 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(morpholin-4-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 4.1 (br d, 2), 3.8 (br d, 4), 3.7 (br d, 4), 3.0-3.4 (m, 8), 2.9 (br d, 4), 2.5 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(3-(dimethylamino)propyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 7.3-8.5 (m, 6), 2.9-3.7 (m, 14), 2.4 (m, 4), 2.1 (s, 3), 2.2 (s, 6), 1.6 (m, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 2.8-4.2 (m, 14), 2.5 (s, 3), 1.8-2.0 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-methoxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 4.2-4.6 (m, 2), 3.6-3.8 (m, 6), 3.3 (s, 3H, 2.6-2.8 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-ethylpiperazin-1-yl)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 2.9-3.9 (m, 18), 2.5 (s, 3), 1.2 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*',*N*'-di(2-hydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.2-8.5 (m, 6), 4.0-4.6 (m, 4), 3.1-3.4 (m, 4), 1.1 (s, 3), 1.2 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(3-hydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (br d, 1), 9.6 (br d, 1), 7.2-8.5 (m, 6), 4.2-4.5 (m, 4), 3.9 (s, 3), 3.0 -3.4 (m, 2), 2.7 (s, 3), 2.2 (m, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(1-methylethyl)-*N*'-(2-(pyrrolidin-1-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (d, 1), 9.6 (d, 1), 7.3-8.5 (m, 6), 4.7 (m, 2), 3.3-3.8 (m, 13), 2.9 (s, 3), 2.1 (m, 4), 1.3 (m, 6) ppm;

N-(4-chlorophenyl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.5 (s, 1), 9.7 (s, 1), 7.2-8.3 (m, 7), 4.2-4.5 (m, 2), 3-3.9 (m, 8), 2.9 (br d, 4), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,2-dimethyl-2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.2-8.5 (m, 6), 4.2-4.6 (m, 2), 3.9 (s, 3), 3.0-3.3 (m, 2), 2.9 (s, 3), 1.3 (s, 3), 1.2 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-(ethoxycarbonyl)piperidin-1-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 7.3-8.5 (m, 6), 4.2-4.5 (m, 2), 4.0 (q, 2), 3.7 (t, 2), 3.0-3.5 (m, 4), 2.6-2.9 (m, 5), 1.6-2.0 (m, 4), 1.1 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2,3-dihydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (s, 1), 7.3-8.5 (m, 6), 3.8-4.4 (m, 3), 3.7 (s, 3), 2.7-3.5 (m, 11) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(di(2-methoxyethyl)amino)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.7 (s, 1), 7.3-8.4 (m, 6), 4.2-4.5 (m, 2), 3.7 (t,

2), 3.2-3.4 (m, 10), 3.1 (s, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(1-methylpiperidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.8 (br, 1), 9.4 (s, 1), 8.4 (s, 1), 8.2 (s, 1), 8.2 (d, 1), 7.9 (dd, 1), 4.4 (dd, 2), 3.6 (br, 2), 3.1 (br, 2), 2.9 (s, 3), 2.8 (s, 3), 2.4 (br, 2), 2.0 (q, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.2 (2s, 2), 4.4 (s, 2), 3.6 (s, 4), 2.9 (s, 6), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (br, 1), 9.4 (s, 1), 8.4 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (dd, 1), 4.4 (d, 1), 4.3 (d, 1), 3.8 (t, 2), 3.2 (br, 2), 2.8 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-fluorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 10.7 (s, 1), 8.3 (dd, 1), 7.9 (s, 1), 7.8 (m, 1), 7.7 (d, 2), 7.5 (m, 1), 7.4 (d, 2), 3.6 (s, 2), 3.4 (br, 2), 3.0 (br, 6), 2.8 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((((2-hydroxyethoxy)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 9.0 (br s, 2), 8.3 (d, 1), 8.2 (s, 1), 8.0 (s, 1), 7.8 (d, 2), 7.7 (d, 1), 7.4 (d, 2), 4.2(s, 2), 3.7 (m, 2), 3.5 (m, 4), 3.2 (br s, 2) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (d, 1), 8.3 (s, 1), 8.0 (s, 1), 7.8 (d, 2), 7.6 (d, 1), 7.4 (d, 2), 4.4 (s, 2), 3.8 (br s, 2), 3.5 (m, 14) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-(2-methylpropyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(pyrrolidin-1-yl)-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.8 (s, 1), 9.6 (s, 1), 9.6 (br s, 1), 8.4 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (d, 1), 7.0 (s, 1), 6.9 (s, 1), 4.4 (d, 1), 4.3 (d, 1), 3.8 (m, 2), 3.4 (m, 4), 3.2 (m, 2), 2.8 (s, 3), 1.9 (br s, 4) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-methyl-*N*'-(3-(dimethylamino)propyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide,

trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 7.9 (d, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.4 (d, 2), 4.4 (m, 2), 3.1 (m, 4), 2.8 (s, 9), 2.1 (m, 2) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2,3,4,5,6-pentahydroxyhexyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.1 (s, 1), 10.4 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 7.9 (d, 1), 7.6 (d, 2), 7.5 (dd, 1), 7.3 (d, 2), 4.3 (s, 2), 4.1 (m, 1), 3.9 (m, 1), 3.7 (d, 1), 3.6 (dd, 1), 3.5 (d, 1), 3.4 (dd, 1), 3.3 (m, 2), 3.0 (br, 1), 2.8 (s, 3), 2.5 (s, 1) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(2-hydroxyethyl)-*N'*-(1,1-di(hydroxymethyl)-2-hydroxyethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.7 (br, 1), 8.3 (d, 1), 8.1 (s, 1), 7.9 (d, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.4 (d, 2), 4.3 (s, 2), 3.8 (s, 1), 3.6 (s, 8), 3.5 (s, 1) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(pyridin-2-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.6 (d, 1), 8.4 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (m, 2), 7.6 (d, 1), 7.5 (m, 1), 7.4 (s, 1), 7.2 (s, 1), 4.5 (s, 2), 4.3 (s, 2), 3.9 (s, 3), 2.8 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(1-methylpiperidin-4-yl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (d, 2), 8.0 (s, 1), 7.7 (m, 3), 7.4 (d, 2), 3.6 (m, 2), 3.0 (m, 2), 2.8 (s, 3), 1.8-2.4 (br, 4) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(2-hydroxyethyl)l-*N'*-(2-(morpholin-4-yl)ethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.0 (s, 1), 7.7 (m, 2), 7.4 (d, 2), 4.4 (s, 2), 3.8 (m, 4), 3.5 (m, 3), 3.2 (m, 5) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4-ethylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.1 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 7.9 (d, 2), 7.7 (m, 3), 7.4 (d, 2), 3.6 (s, 2), 3.4 (br, 3), 3.2 (m, 2), 3.0 (m, 3), 2.4 (m, 2), 1.1 (t, 2) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((4-acetylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (d, 1), 8.2 (s, 1), 8.0 (s, 1), 7.7 (m, 3), 7.4 (d, 2), 4.3 (br, 2), 2.8-4.0 (br, 8), 2.0 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-(4-methylpiperazin-1-yl)amino)methyl)thiophen-2-

yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*-methyl-*N'*-(2,3-dihydroxypropyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.1 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 8.0 (d, 2), 7.8 (d, 2), 7.7 (d, 1), 7.4 (d, 2), 4.4 (s, 2), 3.6 (m, 1), 3.5 (m, 1), 3.2-3.4 (br, 3), 2.5 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR(DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.3 (d, 2), 4.4 (s, 2), 3.8 (s, 3), 3.1-3.8 (m, 8), 2.9 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR(DMSO-d_6/TFA) 10.4 (s, 1), 9.4 (s, 1), 8.2 (s, 1), 7.5 (d, 2), 7.3 (d, 2), 7.1 (m, 2), 4.4 (s, 2), 3.1-3.9 (m, 8), 2.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR(DMSO-d_6/TFA) 10.8 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.1 (m, 2), 4.4 (s, 2), 3.0-3.8 (br m, 8), 2.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR(DMSO-d_6/TFA) 10.9 (br s, 1), 9.4 (s, 1), 8.9 (br s, 2), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.3 (s, 1), 7.2 (s, 1), 4.2 (t, 2), 3.8 (s, 3), 3.6 (t, 2), 3.0 (br s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((pyridinium-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR(DMSO-d_6/TFA) 10.9 (br s, 1), 9.4 (s, 1), 9.1 (d, 2), 8.6 (t, 1), 8.3 (s, 1), 8.1 (m, 4), 7.8 (dd, 1), 7.3 (s, 1), 7.2 (s, 1), 5.8 (s, 2), 3.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((pyridinium-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-hydroxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR(DMSO-d_6/TFA) 10.8 (s, 1), 9.4 (s, 1), 9.1 (d, 2), 8.6 (dd, 1), 8.3 (s, 1), 8.2 (m, 3), 8.1 (d, 1), 7.8 (dd, 1), 7.1 (m, 2), 5.9 (s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-hydroxypropyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 7.2-8.3 (m, 6), 4.0-4.5 (m, 2), 3.8 (s, 3), 2.3-3.3 (m, 5), 1.1 (m, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-iminotetrahydrooxazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR

(DMSO-d_6/TFA) 10.9 (s, 1), 9.6 (br s, 1), 9.4 (s, 1), 9.2 (br s, 1), 7.2-8.3 (m, 6), 4.7 (t, 2), 4.6 (s, 2), 3.8 (s, 3), 3.7 (t, 2) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*,*N'*-dimethyl-*N'*-(2-hydroxyethyl)ammonio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt, NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (s, 1), 8.3 (d, 1), 7.9 (s, 1), 7.7 (m, 3), 7.4 (d, 2), 4.6 (s, 2), 3.9 (br m, 2), 3.4 (br m, 2), 3.0 (s, 6) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-4-((*N'*,*N'*-dimethyl-*N'*-(3-hydroxypropyl)ammonio)methyl)-thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt, NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (s, 1), 8.3 (d, 1), 8.0 (s, 1), 7.8 (m, 3), 7.4 (d, 2), 4.5 (s, 2), 3.5 (t, 1), 3.4 (m, 3), 3.0 (s, 6), 1.9 (m, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-chloro-5-(*N'*-methyl-*N'*-(ethoxycarbonyl)methylamino)benzamide, trifluoroacetic acid salt;

N-(4-methylphenyl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]benzamide, trifluoroacetic acid salt;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-amino-5-chlorobenzamide, trifluoroacetic acid salt;

N-(4-chlorophenyl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 12.18 (br s, 1), 10.45 (s, 1), 9.50 (s, 1), 7.75 (s, 1), 7.69 (s, 1), 7.65 (d, 2), 7.39 (d, 1), 7.36 (d, 2) 7.28 (d, 1), 6.98 (d, 1), 6.91 (d, 1), 5.05 (s, 1), 3.85 (s, 3) ppm.

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(2-(dimethylamino)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.4 (d, 1), 7.2 (d, 1), 4.4 (s, 2), 3.8 (s, 3), 3.5 (s, 4), 2.9 (s, 6), 2.8 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((4-(((1,1-di(hydroxymethyl)-2-hydroxyethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 11.2 (s, 1), 10.8 (s, 1), 8.7 (br, 1), 8.4 (d, 1), 8.2 (s, 1), 7.9 (s, 1), 7.7 (m, 3), 7.4 (d, 2), 5.4 (br, 1), 4.3 (s, 2), 3.6 (s, 6) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((3-methyl-2-imino-2,3-dihydroimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.8 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 7.9 (br s, 2), 7.8 (dd, 1), 7.6 (s, 1), 7.3 (dd, 2), 7.0 (dd, 2), 5.0 (s, 2), 3.9 (s, 3), 3.4 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((1,4,5,6-tetrahydropyrimidin-1-yl)methyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.3 (s, 1), 8.05 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.3 (s, 1), 7.2 (s, 1), 4.6 (s, 2), 3.9 (s, 3), 3.2 (bm, 4), 1.8 (bm, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(hydroxy)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO- d_6/TFA-d) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (dd, 1), 7.9 (dd, 1), 7.7 (d, 1), 7.3 (dd, 2), 4.4 (s, 2), 3.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-aminoethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (d, 1), 9.2 (br s, 1), 8.4 (d, 1), 8.2 (d, 1), 8.1 (s, 1), 7.8~8.0 (m, 2), 7.4 (d, 1), 7.3 (d, 1), 4.3 (s, 2), 3.9 (s, 3), 3.2~3.4 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(methoxymethyl)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 10.4 (s, 1), 9.4 (d, 1), 8.4 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.9 (dd, 1), 7.4 (d, 1), 7.3 (d, 1), 4.6 (s, 2), 4.55 (s, 2), 3.9 (s, 3), 3.8 (br s, 4), 3.4 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (d, 1), 9.0 (s, 1), 8.6 (d, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.3 (d, 1), 4.6 (s, 2), 3.9 (s, 3), 3.4 (m, 2), 2.6 (m, 2), 1.6 ~1.8 (m, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((5-hydroxymethyl-1-methylimidazol-2-yl)thio)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (d, 1), 8.4 (d, 1), 8.1 (d, 1), 7.7 (dd, 1), 7.6 (s, 1), 7.5 (s, 1), 7.3 (d, 1), 7.2 (d, 1), 4.5 (s, 2), 4.3 (s, 2), 3.9 (s, 3), 3.6 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-(((imidazol-2-yl)thio)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.6 (s, 2), 7.5 (s, 1), 7.3 (d, 1), 7.2 (d, 1), 4.4 (s, 2), 3.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide and *N*-(5-chloropyridin-2-yl)-2-[((4-((5-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (2:1 mixture), trifluoroacetic acid salt; NMR (DMSO-d_6) 10.77 (s, 0.3), 10.75 (s, 0.7), 9.37 (s, 0.3), 9.36 (s, 0.7), 9.04 (d, 0.7), 9.01 (d, 0.3), 8.32 (d, 1), 8.06 (d, 1), 7.98 (s, 0.7), 7.88 (dd, 1), 7.80 (s, 0.3), 7.45 (t, 0.3), 7.38 (t, 0.7), 7.35 (m, 1), 7.26

(d, 1), 5.36 (s, 0.6), 5.34 (s, 1.4), 3.84 (s, 3), 2.23 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((4-(hydroxymethyl)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide and *N*-(5-chloropyridin-2-yl)-2-[((4-((5-(hydroxymethyl)imidazol-1-yl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (2:1 mixture), trifluoroacetic acid salt; NMR (DMSO-d_6) 10.78 (s, 0.4), 10.77 (s, 0.6), 9.37 (s, 1), 9.10 (d, 0.6), 9.01 (d, 0.4), 8.32 (d, 1), 8.06 (dd, 1), 8.00 (s, 0.6), 7.88 (dd, 1), 7.81 (s, 0.4), 7.58 (s, 0.4), 7.52 (s, 0.6), 7.36 (m, 1), 7.26 (m, 1), 5.40 (s, 0.8), 5.38 (s, 1.2), 4.50 (s, 0.8), 4.47 (s, 1.2), 3.84 (1, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(imino(pyridin-4-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 10.90 (s, 1), 10.38 (t, 1), 9.85 (s, 1), 9.70 (b, 1), 9.53 (s, 1), 9.40 (s, 1), 8.85 (ddd, 2), 8.35 (d, 1), 8.08 (d, 1), 7.95 (s, 1), 7.90 (dd, 1), 7.70 (ddd, 2), 7.38 (d, 1), 7.25 (d, 1), 4.60 (d, 2), 3.83 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(imino(pyrazin-2-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.90 (s, 1), 10.60 (b, 1), 10.00 (s, 1), 9.70 (s, 1), 9.40 (d, 2), 9.00 (d, 1), 8.90 (d, 1), 8.30 (d, 1), 8.10 (d, 1), 7.90 (s, 1), 7.85 (dd, 1), 7.30 (d, 1), 7.25 (d, 1), 4.65 (d, 2), 3.80 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-(2-(imidazol-4-yl)ethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 10.90 (s, 1), 9.40 (s, 1), 9.00 (s, 1), 8.35 (d, 1), 8.10 (d, 1), 8.00 (s, 1), 7.90 (dd, 1), 7.50 (s, 1), 7.40 (s, 1), 7.25 (s, 1), 4.20 (s, 2), 3.80 (s, 3), 3.30 (t, 2), 3.00 (t, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2,4-dimethylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide and *N*-(5-chloropyridin-2-yl)-2-[((4-((2,5-dimethylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (9:1 mixture), trifluoroacetic acid salt; NMR (DMSO-d_6) 10.90 (s, 1), 9.42 (s, 0.2), 9.40 (s, 0.8), 8.35 (d, 1), 8.10 (d, 1), 7.90 (m, 2), 7.40 (d, 0.2), 7.35 (d, 1), 7.25 (d, 1), 7.20 (d, 0.8), 5.30 (s, 0.4), 5.25 (s, 1.6), 3.80 (s, 3), 2.58 (s, 2.5), 2.54 (s, 0.5), 2.18 (d, 2.5), 2.13 (d, 0.5) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(*N*'-amino-*N*'-methylamino)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 10.80 (s, 1), 9.30 (s, 1), 8.30 (d, 1), 8.20 (s, 1), 8.05 (dd, 1), 7.90 (dd, 1), 7.80 (s, 1), 7.35 (dd, 1), 7.25 (d, 1), 4.90 (s, 2), 3.80 (s, 3), 3.65 (t, 2), 3.50 (t, 2), 3.15 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-aminoimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 12.20 (s, 1), 11.30 (b, 1), 11.10 (s, 1), 8.35 (d, 1), 8.20 (d, 1), 8.10 (s, 1), 7.90 (m, 2), 7.70 (b, 2), 7.60 (s, 1), 7.55 (dd, 1), 6.85 (s, 1), 6.80 (s, 1), 5.05 (s, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(methylthio)imidazolin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 10.1 (s, 1), 9.4 (s, 1), 8.3 (s, 1), 8.1 (d, 1), 7.9 (s, 1), 7.8 (d, 1), 7.3 (s, 1), 7.2 (s, 1), 4.6 (s, 2), 3.8 (s, 3), 3.8 (s, 4), 2.6 (S, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((imidazolin-2-yl)thio)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.6 (s, 1), 10.3 (s, 2), 9.4 (s, 1), 8.3 (s, 1), 8.1 (d, 1), 7.9 (s, 1), 7.8 (d, 1), 7.4 (s, 1), 7.3 (s, 1), 4.5 (s, 2), 3.8 (s, 3), 3.8 (S, 4) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-(methylamino)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (d, 1), 8.4 (d, 1), 8.1 (d, 1), 8.1 (d, 1), 7.8 (d, 1), 7.7 (d, 1), 7.3 (d, 1), 7.2 (d, 1), 4.6 (d, 2), 3.9 (s, 3), 3.6 (m, 2), 2.9~3.2 (m, 5), 2.2 (m, 2) ppm; and

N-(5-chloropyridin-2-yl)-2-[((4-((2-(ethylamino)imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (d, 1), 8.3 (d, 1), 8.1 (d, 2), 7.8 (d, 1), 7.6 (s, 1), 7.35 (s, 1), 7.3 (s, 1), 7.0 (s, 1), 6.9 (s, 1), 5.1 (s, 2), 3.9 (s, 3), 3.2 (m, 2), 1.2 (t, 3) ppm.

E. To methylamine (2.0 M in tetrahydrofuran, 16 mL, 32 mmol) was added a solution of *N*-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide (3.0 g, 6.3 mmol) in DMF (10 mL) and the mixture stirred at ambient temperature. After 4 hours the reaction mixture was poured into water (100 mL), concentrated *in vacuo* to remove the tetrahydrofuran and extracted with ethyl acetate (2x75 mL). The combined organics were washed with brine (75 mL), dried over $MgSO_4$ and concentrated of all volatiles *in vacuo*. Purification by flash chromatography on silica gel afforded 1.1g (38% yield) of *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide as a yellow solid; NMR (DMSO-d_6/TFA) 11.4 (s, 1), 11.0 (s, 1), 8.9 (br s, 2), 7.6-8.4 (m, 7), 4.2 (m, 2), 2.6 (m, 3) ppm.

F. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCl_3$) 9.8 (br, 1), 9.1 (br, 1), 8.3 (d, 1), 7.9 (d, 1),

7.6 (dd, 1), 7.5 (s, 1), 7.1 (d, 1), 7.0 (d, 1), 3.9 (s, 3), 3.7 (s, 2), 2.4 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-methylpiperazin-1-yl)-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.0 (s, 1), 9.6 (s, 1), 9.0 (s, 1), 8.3 (s, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.4 (d, 2), 4.1 (s, 2), 3.5 (d, 2), 3.3 (d, 2), 3.1 (d, 4), 2.8 (s, 3), 2.6 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl) -5-chlorobenzamide; NMR (DMSO-d_6) 8.3 (s, 1), 8.1 (d, 1), 7.9 (s, 2), 7.8 (dd, 1), 7.6 (br, 1), 7.4 (s, 2), 7.3 (br, 1), 3.6 (s, 2), 2.9 (br, 8), 2.3 (s, 3), 1.4 (s, 9) ppm;

5-(*N*-(5-chloropyridin-2-yl)amino)carbonyl-6-[4-(((methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl]amino-1,3-benzodioxole;

N-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.6 (s, 1), 7.2-8.4 (m, 6), 4.4 (s, 2), 3.7 (m, 4), 3.3 (m, 4), 2.9 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((ethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((ethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide;

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((-1,2,4-oxadiazol-3-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.6 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 3.9 (s, 3), 3.8 (s, 2), 3.6 (s, 2), 2.2 (s, 3) ppm.

G. A suspension of *N*-(4-chlorophenyl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide (0.70 g, 1.6 mmol), *N*-hydroxy-*N*-methylamine hydrochloride (0.26 g, 3.2 mmol), K_2CO_3 (0.94 g, 3.2 mmol) and triethylamine (0.88 mL, 6.4 mmol) in DMF (30 mL) was stirred at ambient temperature. After 16 hours, the mixture was poured onto ice water (200 mL) and the resulting precipitate collected by filtration. Purification by HPLC on a C18 Dynamax column with acetonitrile in water gradient with 0.1% trifluoroacetic acid afforded *N*-(4-chlorophenyl)-2-[((3-chloro-4-((*N*'-methyl-*N*'-hydroxyamino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt as a white solid; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (d, 1), 8.2 (s, 1), 7.9 (s, 1), 7.7 (d, 2), 7.6 (d, 1), 7.4

(d, 2), 4.6 (d, 1), 4.5 (d, 1), 3.1 (s, 3) ppm.

H. In a similar manner, the following compound was prepared:

N-(5-chloropyridin-2-yl)-2-[((4-(*N'*-methyl-*N''*-aminoguanidino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (s, 1), 8.1 (d, 1), 7.8 (d, 1), 7.7 (s, 1), 7.4 (s, 2), 7.3 (s, 1), 7.2 (s, 1), 4.6 (s, 2), 3.8 (s, 3) ppm.

I. To a solution of *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.20 g, 0.4 mmol) in DMF (5 mL) were added methyl 2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxylate (0.12 g, 0.48 mmol) and diisopropylethylamine (0.10 g, 0.8 mmol). The mixture was stirred at ambient temperature for 16 hours, and then poured onto brine (10 mL) and extracted with ethyl acetate (3x25 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica gel afforded 0.26 g (92% yield) of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(4-trifluoromethyl-5-(methoxycarbonyl)pyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 7.3-8.9 (m, 7), 4.9 (m, 2), 3.9 (s, 3), 3.8 (s, 3), 3.2 (s, 3) ppm.

J. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(4-trifluoromethyl-5-(methoxycarbonyl)pyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 7.3-9 (m, 7), 4.9 (s, 2), 3.8 (s, 3), 3.8 (br s, 4), 3.2 (s, 3), 2.9 (br s, 4), 2.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-ethyl-*N'*-(4-methyloxazolin-2-yl)amino)methyl-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCl_3$) 9.0 (s, 1), 8.6 (s, 1), 8.3 (d, 1), 8.2 (d, 1), 7.6 (d, 1), 7.4 (s, 1), 7.3 (d, 1), 7.1 (s, 1), 4.4 (m, 3), 4.1 (m, 1), 3.9 (s, 3), 3.8 (t, 1), 3.3 (q, 2), 1.2 (d, 3), 1.1 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(cyanomethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 3.9 (s, 3), 3.7 (s, 2), 3.5 (s, 2), 2.2 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(4-(ethoxycarbonyl)oxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.9 (s, 1), 9.5 (s, 1), 9.4 (s, 1), 8.2 (d, 1), 8.1 (d, 2), 7.9 (dd, 1), 7.6 (m, 2), 7.2 (s, 2), 4.6 (s, 2), 3.9 (t, 2), 3.8 (s, 3), 3.4 (t, 2) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(4-(ethoxycarbonyl)oxazolin-2-yl)amino)methyl)-3-

chlorothiophen-2-yl)carbonyl)amino]-3-(morpholin-4-yl)-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.5 (s, 1), 8.3 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (s, 1), 7.7 (dd, 1), 7.55 (m, 1), 7.3 (m, 2), 5.6 (s, 1), 5.4 (s, 1), 4.4 (s, 2), 4.1 (q, 2), 3.6 (m, 4), 2.95 (s, 2), 2.9 (m, 4), 1.2 (t, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((3-((methylthio)methyl)-1,2,4-oxadiazol-5-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 4.0 (s, 2), 3.9 (s, 3), 3.8 (s, 2), 3.6 (s, 2), 2.3 (s, 3), 2.1 (s, 3) ppm; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-((3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)methyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (s, 1), 7.4 (d, 1), 7.2 (d, 1), 4.5 (s, 2), 4.0 (s, 2), 3.9 (s, 3) ppm. 3.6 (s, 2), 3.3 (s, 3), 2.3 (s, 3) ppm.

K. In a manner similar to that described in Paragraph I above, *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (1.5 g, 3 mmol) reacted with 2-chloro-5-methyl-4,5-dihydrooxazoline (2.7 g, 23 mmol) and triethylamine (0.78 mL, 5.6 mmol) to afford *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(5-methyl-4,5-dihydrooxazolin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide. Purification by HPLC on a C18 Dynamax column with 20-80% acetonitrile in water gradient with 0.1% trifluoroacetic acid afforded the trifluoroacetic acid salt as a white solid: NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.5 (s, 1), 7.4 (s, 1), 7.3 (s, 1), 4.4 (s, 2), 4.2 (m, 1), 3.8 (s, 3), 3.2 (m, 2), 2.8 (s, 3), 1.4 (d, 3) ppm.

L. In a similar manner, the following compound was made:
N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(3,4-dihydro-2*H*-pyrrol-5-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (d, 1), 8.2 (br s, 1), 8.1 (d, 1), 8.0 (br s, 1), 7.7 (dd, 1), 7.4 (d, 1), 7.3 (d, 1), 4.6 (s, 2), 3.9 (s, 3), 3.1 ~3.3 (m, 6) ppm.

M. To a solution of *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.50 g, 1.0 mmol) in DMF (5 mL) were added 2-fluoropyridine (1 mL, 12 mmol) and cesium carbonate (0.33 g, 1.0 mmol) and the mixture was heated at 125°C. After 72 hours the mixture was cooled to ambient temperature, filtered and acidified with aqueous trifluoroacetic acid. Purification by HPLC on a C18 Vydac column with acetonitrile in water gradient with 0.1% trifluoroacetic acid afforded *N*-

(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(pyridin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt as a white solid: NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 8.0-7.9 (m, 3), 7.8 (dd, 1), 7.7 (s, 1), 7.4 (s, 1), 7.2 (d, 1), 7.1 (d, 1), 6.9 (t, 1), 4.8 (s, 2), 3.8 (s, 3), 3.2 (s, 3) ppm.

N. To a suspension of *N*-(4-chlorophenyl)-2-[((4,5-di(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide (0.075 g, 0.14 mmol) in acetonitrile (3 mL) in a pressure vessel was added propylamine (0.025 mL, 0.30 mmol). The vessel was sealed and the suspension heated at 50°C for 10 days, with additional 0.025 mL portions of propylamine being added after 3 and 9 days. The mixture was cooled to ambient temperature and concentrated of all volatiles *in vacuo*. The resulting solid was dissolved in acetonitrile, water and trifluoroacetic acid and purified by HPLC on a C18 Vydac column with 25-60% acetonitrile in water gradient with 0.1% trifluoroacetic acid to afford *N*-(4-chlorophenyl)-2-[((3-chloro-4,5-di((*n*-propyl)aminomethyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt as a white solid; NMR (DMSO-d_6/TFA) 11.3 (s, 1), 10.8 (s, 1), 8.9 (br s, 2), 8.7 (br s, 2), 8.4 (d, 1), 7.4-8.0 (m, 6), 4.6 (s, 2), 4.3 (s, 2), 3.0 (m, 4), 1.6 (m, 4), 0.9 (m, 6) ppm.

O. In a manner similar to that described in Paragraph I above, *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.86 g, 1.7 mmol) reacted with 2-methanesulfonyl-4-aminopyrimidine (0.60 g, 3.5 mmol) and diisopropylethylamine (0.90 mL, 5.2 mmol) in DMSO at 90°C. Purification by chromatography on silica gel afforded 0.78 g (76% yield) of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(4-aminopyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, as a light brown solid; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (dd, 1), 7.8 (d, 1), 7.5 (s, 1), 7.4 (d, 1), 7.3 (d, 1), 6.0 (br s, 1), 5.9 (d, 1), 4.8 (s, 2), 3.9 (s, 3), 3.0 (s, 3) ppm.

P. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(4-aminopyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 10.90 (s, 1H), 9.38 (s, 1H), 8.36 (d, 1H), 8.10 (d, 1H), 7.90 (dd, 1H), 7.69 (s, 1H), 7.62 (d, 1H), 7.38 (d, 1H), 7.28 (d, 1H), 5.96-5.92 (m, 2H), 5.80-5.74 (m, 2H), 4.35 (s, 2H), 3.90 (s, 3H) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(4-(methylamino)pyrimidin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6) 11.90 (br s, 1H), 10.90 (s, 1H), 9.40 (s, 1H), 8.50 (s, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 8.00-7.50 (m, 3H), 7.40 (d, 1H), 7.25 (d, 1H), 6.20-6.00 (m, 2H), 4.60-4.35 (m, 2H), 4.00-3.80 (m, 3H), 2.90-2.80 (m, 3H) ppm.

Q. To a solution of *N*-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (2.1 g, 4.1 mmol) in DMF (20 mL) was added a 2,2,2-trifluoroethylamine (3.2 mL, 41 mmol). The mixture was heated at 75°C for 18 hours, then cooled to ambient temperature and concentrated *in vacuo* to remove excess 2,2,2-trifluoroethylamine. Water was added and the mixture was extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel afforded 2.2 g (95% yield) of *N*-(5-chloropyridin-2-yl)-2-[((4-(((2,2,2-trifluoroethyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 10.8 (s,1) 9.4 (s, 1), 8.2 (d, 1), 8.1 (d, 1), 8.0 (s, 1), 7.8 (dd, 1), 7.2 (d, 2), 4.2 (s, 2), 4.1 (q, 2), 3.8 (s, 3) ppm.

R. To a solution of *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.57 g, 1.1 mmol) in THF (23 mL) was added methyl chlorothiolformate (0.10 mL, 1.15 mmol) at 0°C and the mixture stirred for 2 hours. The reaction was concentrated *in vacuo* and the residue dissolved in ethyl acetate and 1 M HCl. The layers were separated and the organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel afforded 0.26 g (42% yield) of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-((methylthio)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, as a white solid; NMR (DMSO-d_6) 10.9 (s, 1), 9.4 (s, 1), 8.4 (d, 1), 8.1 (d, 1), 7.9 (d, 1), 7.6 (s, 1), 7.4 (s, 1), 7.2 (s, 1), 4.4 (s, 2), 3.9 (s, 3), 3.0 (s, 3), 2.2 (s, 3) ppm.

S. In a similar manner, the following compound was made:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-ethyl-*N*'-((phenylthio)carbonyl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; NMR ($CDCl_3$) 9.0 (s, 1), 8.8 (s, 1), 8.2 (d, 1), 8.1 (d, 1), 7.6 (d, 1), 7.5 (m, 3), 7.4 (m, 3), 7.0 (s, 1), 4.6 (s, 2), 3.9 (s, 3), 3.5 (q, 2), 1.2 (m, 3) ppm.

T. In a manner similar to that described in Paragraph C above, DMF (6 mL) was added to a mixture of *N*-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.87 g, 1.73 mmol) and imidazole (0.35 g, 5.18 mmol) at ambient temperature. The mixture was heated at 45°C for 15 hours. After cooling, additional imidazole (0.25 g, 3.67 mmol) was added, and the heating was continued for 5 days. The mixture was cooled in an ice bath, and trifluoroacetic acid (0.5 mL) was added dropwise. Purification by HPLC on a C18 Dynamax column with 20-70% acetonitrile in water gradient with 0.1% trifluoroacetic acid gave 0.85 g of *N*-(5-chloropyridin-2-yl)-2-[((4-((imidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide,

trifluoroacetic acid salt, as a white solid; NMR (DMSO-d_6/TFA) 10.85 (s, 1), 9.40 (s, 1), 9.20 (s, 1), 8.25 (d 1), 8.05 (d, 1), 7.95 (s, 1), 7.80 (dd, 1), 7.70 (s, 1), 7.60 (s, 1), 7.30 (d, 1), 7.20 (d, 1), 5.40 (s, 2), 3.80 (s, 3) ppm.

U. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((2-methylimidazol-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.85 (s, 1), 9.40 (s, 1), 8.25 (d, 1), 8.05 (d, 1), 7.80 (m, 2), 7.50 (s, 2), 7.30 (d, 1), 7.20 (d, 1), 5.30 (s, 2), 3.80 (s, 3), 2.60 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(1,2,4-triazol-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 10.3 (s., 1), 9.4 (s, 1), 9.2 (s, 1), 8.4 (d, 1), 8.1 (m, 2), 7.9 (m, 1), 7.3 (d, 1), 7.2 (d, 1), 5.6 (s, 2), 3.9 (s, 3), ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2,6-diaminopurin-9-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt, and *N*-(5-chloropyridin-2-yl)-2-[((4-((2,6-diaminopurin-7-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 10.90 (s, 0.5), 10.85 (s, 0.5), 9.40 (s, 0.5), 9.38 (s, 0.5), 8.50 (b, 0.6), 8.34 (m, 1), 8.18 (b, 0.4), 8.14 (s, 1), 8.04-8.09 (m, 2), 7.94 (b, 1), 7.88 (dd, 1), 7.72 (b, 0.4), 7.56 (s, 0.6), 7.36 (m, 2), 7.26 (dd, 1), 5.28 (s, 1), 5.20 (s, 1), 3.85 (s, 1.5), 3.84 (s, 1.5) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-1,2-dihydropyrimidin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.85 (s, 1), 9.40 (s, 1), 8.85 (d, 1), 8.50 (d, 1), 8.30 (d, 1), 8.10 (d, 1), 7.80 (dd, 1), 7.75 (s, 1), 7.30 (s, 1), 7.25 (s, 1), 7.05 (dd, 1), 5.25 (s, 2), 3.80 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-imino-1(2*H*)-pyridin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.90 (s, 1), 9.40 (s, 1), 8.60 (b, 2), 8.30 (d, 1), 8.10 (d, 1), 8.00 (d, 1), 7.80-7.90 (m, 2), 7.45 (s, 1), 7.30 (s, 1), 7.25 (s, 1), 7.10 (d, 1), 6.90 (m, 1), 5.30 (s, 2), 3.80 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((3,5-diamino-4*H*-1,2,4-triazol-4-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (s, 1), 8.3 (s, 1), 8.1 (d, 1), 8.1 (s, 1), 7.9 (d, 1), 7.8 (s, 1), 7.3 (s, 1), 7.2 (s, 1), 5 (s, 2), 3.8 (s, 3) ppm;

N-(5-chloropyridin-2-yl)-2-[((4-((2-iminotetrahydrothiazol-3-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR

(DMSO-d_6/TFA-d) 8.3 (s, 1), 8.1 (d, 1), 7.8 (s, 1), 7.8 (dd, 1), 7.3 (dd, 2), 4.7 (s, 2) 3.9 (t, 2), 3.8 (s, 3) 3.5 (t, 2) ppm; and

N-(5-chloropyridin-2-yl)-2-[((4-((4-imino-1(4*H*)-pyridinyl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 10.85 (s, 1), 9.40 (s, 1), 8.30 (d, 1), 8.15 (m, 4), 8.05 (d, 1), 7.90 (s, 1), 7.85 (dd, 1), 7.35 (d, 1), 7.25 (d, 1), 6.80 (d, 2), 5.30 (s, 2), 3.80 (s, 3) ppm.

V. In a similar manner to that described above in Paragraph T, *N*-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.31 g, 0.6 mmol) and pyrazole (0.56 g, 6.7 mmol) were mixed in DMF (20 mL). The mixture was heated at 50°C for 2 days. It was then added to water and the precipitate was isolated by filtration. The solid was dissolved in CH_2Cl_2 (200 mL) and washed with water (2x50 mL) and brine (2x50 mL), dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography using 20:1 CH_2Cl_2:CH_3OH as the eluent and precipitation afforded *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-(pyrazol-3-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, as a white solid; NMR (DMSO-d_6) 11.55 (br s, 1H), 10.90 (s, 1H), 9.35 (s, 1H), 8.36 (d, 1H), 8.10 (d, 1H), 7.90 (dd, 1H), 7.64 (s, 1H), 7.40-7.25 (m, 3H), 5.60 (br s, 1H), 5.50 (s, 1H), 4.20 (s, 2H), 3.85 (s, 3H) ppm.

W. In a manner similar to that described in Paragraph I above, to a solution of 2-methoxy-3,4,5,6-tetrahydropyridine (0.27 g, 2.4 mmol), *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (1.0 g, 2.0 mmol) and DMF (10 mL) at ambient temperature was added *N,N*-diisopropylethylamine (0.65 g, 5.0 mmol). The solution was then warmed to 70°C for 3 days. It was then poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification by HPLC on a C18 Dynamax column with acetonitrile in water gradient with 0.1% trifluoroacetic acid afforded the trifluoroacetic acid salt of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N'*-methyl-*N'*-(3,4,5,6-tetrahydropyridin-2-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, as a white solid; NMR (DMSO-d_6/TFA) 10.9 (s, 1), 9.4 (d, 1), 8.4 (d, 1), 9.2 (br s, 1), 8.3 (d, 1), 8.2 (d, 1), 7.9 (m, 2), 7.4 (d, 1), 7.3 (d, 1), 4.6 (d, 2), 3.9 (s, 3), 2.6~3.4 (7), 1.6 (m, 3) ppm.

X. In a manner similar to that described in Paragraph O above, a mixture of 2-amino-4-chloro-6-methylpyrimidine (0.3 g, 2.1 mmol), *N*-(5-chloropyridin-2-yl)-2-[((4-((methylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide (0.25 g, 0.5 mmol), *N,N*-diisopropylethylamine (0.44 mL, 2.5 mmol), and DMSO (5mL) was

heated under N_2 at 100°C for 15 hours. The mixture was cooled in ice bath, and trifluoroacetic acid (0.5 mL) was added dropwise. Purification by HPLC on a C18 Dynamax column with 20-70% acetonitrile in water gradient with 0.1% trifluoroacetic acid gave 0.24 g of *N*-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-amino-6-methylpyrimidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt, as a white solid; NMR (DMSO-d_6/TFA) 10.85 (s, 1), 9.40 (s, 1), 8.30 (1, 1), 8.10 (d, 1), 7.80 (d, 1), 7.60 (m, 2), 7.30 (s, 1), 7.25 (s, 1), 6.35 (s, 0.3), 6.30 (s, 0.7), 4.80 (s, 1.5), 4.60 (s, 0.5), 3.80 (s, 3), 2.22 (s, 2.2), 2.18 (s, 0.8) ppm.

Y. In a similar manner, the following compounds were made:

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(2-chloropyrimidin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6) 10.85 (s, 1), 9.40 (s, 1), 8.30 (d, 1), 8.10 (d, 1), 8.09 (b, 1), 7.90 (dd, 1), 7.60 (s, 1), 7.35 (s, 1), 7.25 (s, 1), 6.70 (d, 1), 4.65 (b, 2), 3.80 (s, 3), 3.30 (s, 3) ppm; and

N-(5-chloropyridin-2-yl)-2-[((4-((*N*'-methyl-*N*'-(pyridin-4-yl)amino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 10.85 (s, 1), 9.40 (s, 1), 8.30 (d, 1), 8.20 (b, 2), 8.10 (d, 1), 7.80 (dd, 1), 7.60 (s, 1), 7.30 (s, 1), 7.25 (s, 1), 7.00 (d, 2), 4.75 (s, 2), 3.80 (s, 3), 3.20 (s, 3) ppm.

Z. In a manner similar to Paragraph E above, *N*-(5-chloropyridin-2-yl)-2-[((4-(chloromethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide(1.0 g, 2.0 mmol) in DMF (5 mL) was reacted with dimethylamine (1.33 M in tetrahydrofuran, 7.5 mL, 10 mmol) to give *N*-(5-chloropyridin-2-yl)-2-[((4-((dimethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; which was purified by lyophilization from aqueous HCl to afford *N*-(5-chloropyridin-2-yl)-2-[((4-((dimethylamino)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-3-methoxy-5-chlorobenzamide; hydrochloric acid salt, as a white solid; NMR (DMSO- d_6/TFA) 10.9 (s, 1), 10.1 (br s, 1), 9.5 (s, 1), 8.3 (d, 1), 8.2 (s, 1), 8.1 (d, 1), 7.8 (dd, 1), 7.3 (dd, 2), 4.3 (br s, 2), 3.9 (s, 3), 2.8 (br s, 6) ppm.

AA. Other compounds of the invention may be prepared by methods similar to those described in this Example and by methods known to those of ordinary skill in the art.

EXAMPLE 2

Compounds of Formula (Ic)

A. To a suspension of *N*-(4-chlorophenyl)-2-[((5-(bromomethyl)-3-chlorothiophen-2-

yl)carbonyl)amino]-5-chlorobenzamide (0.75 g, 1.5 mmol) in methylene chloride (25 mL) was added 1-methylpiperazine (0.8 mL, 7.3 mmol). The resultant mixture was stirred at ambient temperature for 18 hours, then diluted with methylene chloride. The mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was back-extracted with methylene chloride. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was dissolved in acetonitrile, water and trifluoroacetic acid. Purification by HPLC on a C18 Dynamax column with 20-80% acetonitrile in water gradient with 0.1% trifluoroacetic acid afforded *N*-(4-chlorophenyl)-2-[((5-((4-methylpiperazin-1-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide, trifluoroacetic acid salt; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.7 (s, 1), 8.3 (d, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.3 (s, 2), 7.2 (dd, 1), 4.5 (s, 2), 3.6-3.2 (br m, 8), 2.8 (s, 3) ppm.

B. In a similar manner to that described in Paragraph A above, *N*-(4-chlorophenyl)-2-[((5-(bromomethyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide (0.5 g, 1.0 mmol) was reacted with thiomorpholine (0.5 mL, 4.8 mmol). Purification by flash chromatography on silica gel afforded 0.4 g (73% yield) of *N*-(4-chlorophenyl)-2-[((5-((thiomorpholin-4-yl)methyl)-3-chlorothiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; as a pale yellow powder; NMR ($CDCl_3$) 11.0 (s, 1), 9.0 (s, 1), 8.2 (d, 1), 7.8 (d, 2), 7.5 (d, 1), 7.4 (d, 2), 7.4 (s, 1), 7.2 (dd, 1), 3.7 (s, 2), 2.8 (m, 4), 2.7 (m, 4) ppm.

C. In a similar manner, the following compounds were made:

N-(4-chlorophenyl)-2-[((3-chloro-5-(((2-(dimethylamino)ethyl)thio)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.1 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 7.9 (s, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.4 (d, 2), 7.2 (s, 1), 4.0 (s, 2), 3.3 (m, 2), 2.8-2.7 (m, 8) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-5-((*N'*-methyl-*N'*-(2-dimethylaminoethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6/TFA) 11.2 (s, 1), 10.8 (s, 1), 8.4 (d, 1), 7.9 (s, 1), 7.7 (d, 2), 7.6 (dd, 1), 7.4 (s, 1), 7.3 (d, 2), 4.6 (s, 2), 3.5 (s, 4), 2.8 (s, 6), 2.7 (s, 3) ppm;

N-(4-chlorophenyl)-2-[((3-chloro-5-((4-(ethoxycarbonylmethyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.2 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 7.3-8.0 (m, 7), 4.4 (s, 2), 4.2 (m, 4), 3.3 (br d, 8), 1.2 (t, 3) ppm;

N-(4-chlorophenyl)-2-[((3-((4-methylpiperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(morpholin-4-yl)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N*'-methyl-*N*'-(2-hydroxyethyl)amino)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N*'-methyl-*N*'-(ethoxycarbonylmethyl)amino)methylthiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(*N*',*N*'-di(2-hydroxyethyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-((4-(((2-(2-methoxyethoxy)ethoxy)methyl)carbonyl)piperazin-1-yl)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-5-(((*N*'-(3-dimethylaminophenyl)amino)methyl)thiophen-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-(pyrrolidin-1-yl)methylbenzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-(dimethylamino)methylbenzamide;

N-(4-chlorophenyl)-2-[((3-(4-methylpiperazin-1-yl)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-fluorophenyl)-2-[((3-chlorobenzo[*b*]thien-2-yl)carbonyl)amino]-5-(amino)methylbenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-(4-methylpiperazin-1-yl)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide;

N-(4-chlorophenyl)-2-[((3-chloro-6-(4-(ethoxycarbonylmethyl)piperazin-1-yl)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide; NMR (DMSO-d_6) 11.4 (s, 1), 10.8 (s, 1), 8.3 (d, 1), 7.4-8.0 (m, 9), 4.1 (m, 2), 3.6 (s, 2), 3.2 (s, 2), 3.1 (m, 1), 2.7 (m, 1), 2.4 (br m, 6), 1.2 (t, 3) ppm.

D. To a suspension of *N*-(4-chlorophenyl)-2-[((3-(bromomethyl)benzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide (0.075 g, 0.14 mmol) in methylene chloride (1.5 mL) in a pressure vessel was added dimethylamine hydrochloride (0.035 g, 0.43 mmol), followed by Bio-Rad AG1-X8 anion exchange resin (0.55 g, 0.7 mmol equivalents, OH^- form). The vessel was sealed and the mixture was stirred at ambient temperature for 3.5 hours. The vessel was opened and the reaction mixture diluted with methylene chloride (25 mL) and acetonitrile (25 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel, followed by crystallization from acetonitrile afforded 0.030 g (43% yield) of *N*-(4-chlorophenyl)-2-[((3-(dimethylamino)methylbenzo[*b*]thien-2-yl)carbonyl)amino]-5-chlorobenzamide, as a crystalline solid; NMR (DMSO-d_6/TFA) 13.2 (s, 1), 10.7 (s, 1), 7.3-8.1 (m, 11), 3.9 (s, 2), 2.1 (s, 6) ppm.